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(71) Applicant (*for all designated States except US*): THE JOHNS HOPKINS UNIVERSITY [US/US]; 111 Market Place, Baltimore, MD 21202 (US).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): ST. CROIX, Brad [CA/US]; 319 Lord Byron Lane #202, Cockeysville, MD 21020 (US). KINZLER, Kenneth, W. [US/US]; 1403 Halkirk Way, BelAir, MD 21015 (US). VOGELSTEIN, Bert [US/US]; 3700 Brenton Way, Baltimore, MD 21208 (US).

(74) Agents: KAGAN, Sarah, A. et al.; Banner & Witcoff, Ltd., 1001 G Street, N.W., Eleventh Floor, Washington, DC 20001-4597 (US).

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(54) Title: ENDOTHELIAL CELL EXPRESSION PATTERNS

(57) Abstract: To gain a better understanding of tumor angiogenesis, new techniques for isolating endothelial cells (ECs) and evaluating gene expression patterns were developed. When transcripts from ECs derived f rom normal and malignant colorectal tissues were compared with transcripts from non-endothelial cells, over 170 genes predominantly expressed in the endothelium were identified. Comparison between normal- and tumor-derived endothelium revealed 79 differentially expressed genes, including 46 that were specifically elevated in tumor-associated endothelium. Experiments with representative genes from this group demonstrated that most were similarly expressed in teh endothelium of primary lung, breast, brain, and pancreatic cancers as well as in metastatic lesions of the liver. These results demonstrate that neoplastic and normal endothelium in humans are distinct at the molecular level, and have significant implications for the development of anti-angiogenic therapies in the future.

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ENDOTHELIAL CELL EXPRESSION PATTERNS

[01] This application claims the benefit of provisional applications serial numbers 60/222,599 filed August 2, 2000, 60/224,360 filed August 11, 2000, and 60/282,850 filed April 11, 2001, the disclosures of which are expressly incorporated herein.

[02] The U.S. government retains certain rights in the invention by virtue of the provisions of National Institutes of Heath grants CA57345 and CA43460, which supported this work.

TECHNICAL FIELD OF THE INVENTION

[03] This invention is related to the area of angiogenesis and anti-angiogenesis. In particular, it relates to genes which are characteristically expressed in tumor endothelial and normal endothelial cells.

BACKGROUND OF THE INVENTION

[04] It is now widely recognized that tumors require a blood supply for expansive growth. This recognition has stimulated a profusion of research on tumor angiogenesis, based on the idea that the vasculature in tumors represents a potential therapeutic target. However, several basic questions about tumor endothelium remain unanswered. For example, are vessels of tumors qualitatively different from normal vessels of the same tissue? What is the relationship of tumor endothelium to endothelium of healing wounds or other physiological or pathological forms of angiogenesis? The answers to these questions critically impact on the potential for new therapeutic approaches to inhibit angiogenesis in a specific manner.

[05] There is a continuing need in the art to characterize the vasculature of tumors relative to normal vasculature so that any differences can be exploited for therapeutic and diagnostic benefits.

[06] One technique which can be used to characterize gene expression, or more precisely gene transcription, is termed serial analysis of gene expression (SAGE). Briefly, the SAGE approach is a method for the rapid quantitative and qualitative analysis of mRNA transcripts based upon the isolation and analysis of short defined sequence tags (SAGE Tags) corresponding to expressed genes. Each Tag is a short nucleotide sequences (9-17 base pairs in length) from a defined position in the transcript. In the SAGE method, the Tags are dimerized to reduce bias inherent in cloning or amplification reactions. (See, US Patent 5,695,937) SAGE is particularly suited to the characterization of genes associated with vasculature stimulation or inhibition because it is capable of detecting rare sequences, evaluating large numbers of sequences at one time, and to provide a basis for the identification of previously unknown genes.

SUMMARY OF THE INVENTION

[07] One embodiment of the invention provides an isolated molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 3, 9, 17, 19, and 44, as shown in SEQ ID NO: 196, 200, 212, 230, 232, and 271, respectively. The molecule can be, for example, an in tact antibody molecule, a single chain variable region (ScFv), a monoclonal antibody, a humanized antibody, or a human antibody. The molecule can optionally be bound to a cytotoxic moiety, bound to a therapeutic moiety, bound to a detectable moiety, or bound to an anti-tumor agent.

[08] According to another embodiment of the invention a method of inhibiting neoangiogenesis is provided. An effective amount of an isolated molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 3, 9, 17, 19, 22, and 44, as shown in SEQ ID NO: 196, 200, 212, 230, 232, 238, and 271, respectively, is administered to a subject in need thereof. Neoangiogenesis is consequently inhibited. The subject may bear a vascularized tumor, may have polycystic kidney disease, may have diabetic retinopathy, may have rheumatoid arthritis, may have psoriasis, for example.

[09] Another aspect of the invention is a method of inhibiting tumor growth. An effective amount of an isolated molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 3, 9, 17, 19, 22, and 44, as shown in SEQ ID NO: 196, 200, 212, 230, 232, 238, and 271, respectively, is administered to a human subject bearing a tumor. The growth of the tumor is consequently inhibited.

[10] Still another aspect of the invention provides an isolated molecule comprising an antibody variable region which specifically binds to a TEM protein selected from the group consisting of: 3, 9, 17, 19, and 44, as shown in SEQ ID NO: 200, 212, 230, 232, and 271, respectively. The molecule can be, for example, an in tact antibody molecule, a single chain variable region (ScFv), a monoclonal antibody, a humanized antibody, or a human antibody. The molecule can optionally be bound to a cytotoxic moiety, bound to a therapeutic moiety, bound to a detectable moiety, or bound to an anti-tumor agent.

[11] According to still another aspect of the invention an isolated and purified human transmembrane protein is provided. The protein is selected from the group consisting of: TEM 3, 9, 17, and 19 as shown in SEQ ID NO: 200, 212, 230, and 232, respectively.

[12] Yet another aspect of the invention is an isolated and purified nucleic acid molecule comprising a coding sequence for a transmembrane TEM selected from the group consisting of: : TEM 3, 9, 17, and 19 as shown in SEQ ID NO: 200, 212, 230, and 232, respectively. The isolated and purified nucleic acid molecule may optionally comprise a coding sequence selected from those shown in SEQ ID NO: : 199, 211, 229, and 231.

[13] Still another aspect of the invention is a recombinant host cell which comprises a nucleic acid molecule. The nucleic acid molecule comprises a coding sequence for a transmembrane TEM selected from the group consisting of: : TEM 3, 9, 17, and 19 as shown in SEQ ID NO: 200, 212, 230, and 232, respectively. The recombinant host cell optionally comprises a coding sequence selected from those shown in SEQ ID NO: 199, 211, 229, and 231.

[14] According to one embodiment of the invention a method is provided for inducing an immune response in a mammal. A nucleic acid molecule comprising a coding sequence for a human transmembrane protein selected from the group consisting of: TEM 1, 3, 9, 13, 17, 19, 22, 30, and 44 as shown in SEQ ID NO: , respectively, is administered to the mammal. An immune response to the human transmembrane protein is thereby induced in the mammal. Optionally the coding sequence is shown in SEQ ID NO: 196, 200, 212, 220, 230, 232, 238, 250 and 271.

[15] According to yet another embodiment of the invention a method of inducing an immune response in a mammal is provided. A purified human transmembrane protein selected from the group consisting of: TEM 1, 3, 9, 13, 17, 19, 22, 30, and 44 as shown in SEQ ID NO: 196, 200, 212, 220, 230, 232, 238, 250 and 271, respectively, is administered to the mammal. An immune response to the human transmembrane protein is thereby induced in the mammal.

[16] Another aspect of the invention is a method for identification of a ligand involved in endothelial cell regulation. A test compound is contacted with an isolated and purified human trasmembrane protein selected from the group consisting of 1, 3, 9, 13, 17, 30, 19, and 44 as shown in SEQ ID NO: 196, 200, 212, 220, 230, 232, 250, and 271. The isolated and purified human trasmembrane protein is also contacted with a molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 3, 9, 13, 17, 30, 19, and 44 as shown in SEQ ID NO: 196, 200, 212, 220, 230, 232, 250, and 271 respectively. Binding of the molecule comprising an antibody variable region to the human transmembrane protein is determined. A test compound which diminishes the binding of the molecule comprising an antibody variable region to the human transmembrane protein is identified as a ligand involved in endothelial cell regulation.

[17] Yet another aspect of the invention is a method for identification of a ligand involved in endothelial cell regulation. A test compound is contacted with a cell comprising a human transmembrane protein selected from the group consisting of 1, 3, 9, 17, and 19 as shown in SEQ ID NO: 196, 200, 212, 230, and 232. The cell is also contacted with a molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 3, 9, 17, and 19 as shown in SEQ ID NO: 196, 200, 212, 230, and 232 , respectively. Binding of the molecule comprising an antibody variable region to the cell is determined. A test compound which diminishes the binding of the molecule comprising an antibody variable region to the cell is identified as a ligand involved in endothelial cell regulation.

[18] Yet another aspect of the invention is a method for identification of a ligand involved in endothelial cell regulation. A test compound is contacted with a human transmembrane protein selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27,

28, 29, 40, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 223 & 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 358, 257, 259, 261, 263, 267, 269, 271, 273, and 275. Binding of a test compound to the human transmembrane protein is determined. A test compound which binds to the protein is identified as a ligand involved in endothelial cell regulation.

[19] Another embodiment of the present invention is a soluble form of a human transmembrane protein selected from the group consisting of: TEM 1, 3, 9, 17, 19, 22, 30, and 44 as shown in SEQ ID NO: 196, 200, 212, 230, 232, 238, 250, and 271 respectively. The soluble forms lack transmembrane domains. The soluble form may consist of an extracellular domain of the human transmembrane protein.

[20] Also provided by the present invention is a method of inhibiting neoangiogenesis in a patient. A soluble form of a human transmembrane protein is adminstered to the patient. Neoangiogenesis in the patient is consequently inhibited. The patient may bear a vascularized tumor, may have polycystic kidney disease, may have diabetic retinopathy, may have rheumatoid arthritis, or may have psoriasis, for example.

[21] Another embodiment of the invention provides a method of inhibiting neoangiogenesis in a patient. A soluble form of a human transmembrane protein is administered to the patient. Neoangiogenesis in the patient is consequently inhibited. The patient may bear a vascularized tumor, may have polycystic kidney disease, may have diabetic retinopathy, may have rheumatoid arthritis, or may have psoriasis, for example.

[22] According to still another aspect of the invention a method of identifying regions of neoangiogenesis in a patient is provided. A molecule comprising an antibody variable region which specifically binds to an

extracellular domain of a TEM protein selected from the group consisting of: 1, 3, 9, 13, 17, 19, 22, 30, and 44, as shown in SEQ ID NO: 196, 200, 212, 220, 230, 232, 238, 250, and 271, respectively, is administered to a patient. The molecule is bound to a detectable moiety. The detectable moiety is detected in the pateint, thereby identifying neoangiogenesis.

[23] According to another aspect of the invention a method is provided for inducing an immune response to tumor endothelial cells in a patient. A mouse TEM protein selected from the group consisting of: 1, 2, 3, 9, 13, 17, 19, 22, and 30 as shown in SEQ ID NO: 291, 293, 299, 295, 303, 297, 301, 305, and 307, is administered to a patient in need thereof. An immune response to a human TEM protein is consequently induced.

[24] Still another embodiment of the invention is a method of screening for neoangiogenesis in a patient. A body fluid collected from the patient is contacted with a molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 3, 9, 17, 19, and 44, as shown in SEQ ID NO: 196, 200, 212, 230, 232, and 271, respectively. Detection of cross-reactive material in the body fluid with the molecule indicates neo-angiogenesis in the patient.

[25] Still another embodiment of the invention provides a method of inhibiting neoangiogenesis in a patient. A molecule comprising an antibody variable region which specifically binds to a TEM protein selected from the group consisting of: 4, 6, 7, 10, 12, 14, 20, 25, 27, 31, 36, 37, 38, 39, and 40 as shown in SEQ ID NO: 202, 206, 208, 214, 218, 223 and 224, 234, 242, 244, 252, 257, 259, 261. 263, and 265, is administered to the patient. Neoangiogenesis in the patient consequently inhibited.

[26] Yet another aspect of the invention is a method of screening for neoangiogenesis in a patient. A body fluid collected from the patient is

contacted with a molecule comprising an antibody variable region which specifically binds to a TEM protein selected from the group consisting of: 4, 6, 7, 10, 12, 14, 20, 25, 27, 31, 36, 37, 38, 39, and 40, as shown in SEQ ID NO: 202, 206, 208, 214, 218, 223 & 224, 234, 242, 244, 252, 257, 259, 261. 263, and 265, respectively. Detection of cross-reactive material in the body fluid with the molecule indicates neoangiogenesis in the patient.

[27] Also provided by the present invention is a method of promoting neoangiogenesis in a patient. A TEM protein selected from the group consising of: 4, 6, 7, 10, 12, 14, 20, 25, 27, 31, 36, 37, 38, 39, and 40, as shown in SEQ ID NO: 202, 206, 208, 214, 218, 223 & 224, 234, 242, 244, 252, 257, 259, 261. 263, and 265, is administered to a patient in need of neoangiogenesis. Neoangiogenesis in the patient is consequently stimulated.

[28] One embodiment of the invention provides a method of promoting neoangiogenesis in a patient. A nucleic acid molecule encoding a TEM protein selected from the group consising of: 4, 6, 7, 10, 12, 14, 20, 25, 27, 31, 36, 37, 38, 39, and 40, as shown in SEQ ID NO: 201, 205, 207, 213, 217, 221 & 222, 233, 241, 243, 251, 256, 258, 260, 262, and 264, is administered to a patient in need of neoangiogenesis. The TEM protein is consequently expressed and neoangiogenesis in the patient is stimulated.

[29] Another embodiment of the invention provides a method of screening for neoangiogenesis in a patient. A TEM protein selected from the group consisting of: 4, 6, 7, 10, 12, 14, 20, 25, 27, 31, 36, 37, 38, 39, and 40, as shown in SEQ ID NO: : 202, 206, 208, 214, 218, 223 & 224, 234, 242, 244,.252, 257, 259, 261. 263, and 265, respectively, is detected in a body fluid collected from the patient. Detection of the TEM protein indicates neoangiogenesis in the patient.

[30] Another aspect of the invention is a method of screening for neoangiogenesis in a patient. A nucleic acid encoding a TEM protein

selected from the group consisting of: 4, 6, 7, 10, 12, 14, 20, 25, 27, 31, 36, 37, 38, 39, and 40 is detected in a body fluid collected from the patient. The nucleic acid is selected from the group consisting of those shown in SEQ ID NO: 201, 205, 207, 213, 217, 221 & 222, 233, 241, 243, 251, 256, 258, 260, 262, and 264. Detection of the TEM protein indicates neoangiogenesis in the patient.

[31] Yet another embodiment of the invention is an isolated and purified nucleic acid molecule which encodes a NEM protein selected from the group consisting of: 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289. The nucleic acid molecule optionally comprises a coding sequence as shown in SEQ ID NO: 278, 282, 284, and 288. The nucleic acid may be maintained in a recombinant host cell.

[32] The present invention also provides an isolated and purified NEM protein selected from the group consising of: 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289.

[33] The present invention further provides an isolated molecule comprising an antibody variable region which specifically binds to a NEM protein selected from the group consisting of: 14, 22, 23, and 33, as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289.

[34] An additional embodiment of the present invention is a method of inhibiting neoangiogenesis. An effective amount of a NEM protein selected from the group consising of: 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289 is administered to a subject in need thereof . Neoangiogenesis is thereby inhibited.

[35] A still further embodiment of the invention is a method to identify candidate drugs for treating tumors. Cells which express one or more TEM genes selected from the group consisting of: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11,

12, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 40, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: : 195, 197, 199, 201, 203, 205, 207, 209, 211, 213, 215, 217, 221 & 222, 225, 227, 229, 231, 233, 235, 237, 239, 241, 243, 245, 247, 249, 251, 253, 255, 256, 258, 260, 262, 266, 268, 270, 272, and 274, respectively, are contacted with a test compound. Expression of said one or more TEM genes is determined by hybridization of mRNA of said cells to a nucleic acid probe which is complementary to said mRNA. A test compound is identified as a candidate drug for treating tumors if it decreases expression of said one or more TEM genes. Optionally the cells are endothelial cells. Alternatively or additionally, the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more TEMs. Test compounds which increase expression can be identified as candidates for promoting wound healing.

[36] Yet another embodiment of the invention is a method to identify candidate drugs for treating tumors. Cells which express one or more TEM proteins selected from the group consisting of: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 40, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 223 & 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 358, 257, 259, 261, 263, 267, 269, 271, 273, and 275, respectively, are contacted with a test compound. The amount of said one or more TEM proteins in said cells is determined. A test compound is identified as a candidate drug for treating tumors if it decreases the amount of one or more TEM proteins in said cells. Optionally the cells are endothelial cells. Alternatively or additionally, the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more TEMs. Alternatively, a test compound which increases the amount of one or more TEM proteins in said cells is identified as a candidate drug for treating wound healing.

[37] According to another aspect of the invention a method is provided to identify candidate drugs for treating tumors. Cells which express one or more TEM proteins selected from the group consisting of: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 40, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 223 & 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 358, 257, 259, 261, 263, 267, 269, 271, 273, and 275, respectively, are contacted with a test compound. Activity of said one or more TEM proteins in said cells is determined. A test compound is identified as a candidate drug for treating tumors if it decreases the activity of one more TEM proteins in said cells. Optionally the cells are endothelial cells. Alternatively or additionally, the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more TEMs. Optionally the cells are endothelial cells. If a test compound increases the acitivity of one more TEM proteins in said cells it can be identified as a candidate drug for treating wound healing.

[38] An additional aspect of the invention is a method to identify candidate drugs for treating patients bearing tumors. A test compound is contacted with recombinant host cells which are transfected with an expession construct which encodes one or more TEM proteins selected from the group consisting of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 40, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 223 & 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 358, 257, 259, 261, 263, 267, 269, 271, 273, and 275, respectively. Proliferation of said cells is determined. A test compound which inhibits proliferation of said cells is identified as a candidate drug for treating patients bearing tumors. A test coumpound which stimulates

proliferation of said cells is identified as a candidate drug for promoting neoangiogenesis, such as for use in wound healing.

[39] Another embodiment of the invention provides a method to identify candidate drugs for treating tumors. Cells which express one or more NEM genes selected from the group consisting of: 14, 22, 23, and 33 as shown in SEQ ID NO: 278, 282, 284, and 288, respectively, are contacted with a test compound. Expression of said one or more NEM genes is determined by hybridization of mRNA of said cells to a nucleic acid probe which is complementary to said mRNA. A test compound is identified as a candidate drug for treating tumors if it increases expression of said one or more NEM genes. Optionally the cells are endothelial cells. Alternatively or additionally, the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more NEMs.

[40] According to another aspect of the invention a method is provided to identify candidate drugs for treating tumors. Cells which express one or more NEM proteins selected from the group consisting of: 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289, are contacted with a test compound. The amount of said one or more NEM proteins in said cells is determined. A test compound is identified as a candidate drug for treating tumors if it increases the amount of one more NEM proteins in said cells. Optionally the cells are endothelial cells. Alternatively or additionally, the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more NEMs.

[41] An additional aspect of the invention is a method to identify candidate drugs for treating tumors. Cells which express one or more NEM proteins selected from the group consisting of: 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289, are contacted with a test compound. Activity of said one or more NEM proteins in said cells is determined. A test compound is identified as a candidate drug for treating

tumors if it increases the activity of said one or more NEM proteins in said cells. Optionally the cells are endothelial cells. Alternatively or additionally, the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more NEMs.

[42] Still another embodiment of the invention provides a method to identify candidate drugs for treating patients bearing tumors. Atest compound is contacted with recombinant host cells which are transfected with an expession construct which encodes one or more NEM proteins selected from the group consisting of 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289. Proliferation of said cells is determined. A test compound which stimulates proliferation of said cells is identified as a candidate drug for treating patients bearing tumors.

[43] Another aspect of the invention is a method for identifying endothelial cells. One or more antibodies which bind specifically to a TEM or NEM protein selected from the group consisting of TEM : 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 30, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 223 & 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 358, 257, 259, 261, 263, 267, 269, 271, 273, and 275 and NEM 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289, is contacted with a population of cells. Cells in the population which have bound to said antibodies are detected. Cells which are bound to said antibodies are identified as endothelial cells. Optionally cells which have bound to said antibodies are isolated from cells which have not bound.

[44] Still another aspect of the invention is a method for identifying endothelial cells. One or more nucleic acid hybridization probes which are complementary to a TEM or NEM gene nucleic acid sequence selected from the group consisting of of TEM : 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16,

17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 30, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 223 & 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 358, 257, 259, 261, 263, 267, 269, 271, 273, and 275 and NEM 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289, is contacted with nucleic acids of a population of cells. Nucleic acids which have specifically hybridized to said nucleic acid hybridization probes are detected. Cells whose nucleic acids specifically hybridized are identified as endothelial cells.

[45] Yet another embodiment of the invention is a method of inhibiting neoangiogenesis. An effective amount of an isolated molecule comprising an antibody variable region which specifically binds to an extracellular domain of a mouse TEM protein selected from the group consisting of: 1, 2, 3, 9, 17, and 19, as shown in SEQ ID NO: 291, 293, 299, 295, 297, and 301, respectively, is administered to a subject in need thereof . Neoangiogenesis is thereby inhibited. The subject may be a mouse, may bear a vascularized tumor, may have polycystic kidney disease, may have diabetic retinopathy. may have rheumatoid arthritis, or may have psoriasis, for example.

[46] These and other embodiments which will be apparent to those of skill in the art upon reading the specification provide the art with reagents and methods for detection, diagnosis, therapy, and drug screening pertaining to neoangiogenesis and pathological processes involving or requiring neoangiogenesis.

BRIEF DESCRIPTION OF THE DRAWINGS

[47] Fig. 1A-1B. vWF expression in colorectal cancers. vWF (red stain) was detected in vessels by in situ hybridization. At low power magnification (Fig. 1.A) vessels were often surrounded by a perivascular cuff of viable cells

(red arrows), with a ring of necrotic cells evident at the periphery (black arrows). At high power magnification (Fig. 1.B) the expression of vWF (red) was clearly localized to the vessels. Sections were counterstained with methyl green.

[48] Fig. 2A-2D. Purification of Endothelial Cells (ECs) from human normal and malignant tissue. (Fig. 2A) Vessels (red) of frozen sections were stained by immunofluorescence with the P1H12 monoclonal antibody (Chemicon, Temecula, CA) and detected using a biotinylated goat anti-mouse IgG secondary antibody followed by rhodamine-linked strepavidin. The region stained is from within the lamina propria of normal colonic mucosa. Note that the larger vessels (arrowheads) and capillaries (arrows) are positive, and staining of hematopoietic cells was undetectable. E-cadherin positive epithelial cells (green) at the edge of the crypt were simultaneously visualized using a rabbit polyclonal antibody (Santa Cruz, Santa Cruz, CA), followed by a goat anti-rabbit IgG secondary antibody labelled with alexa (Molecular Probes, Eugene, OR). Sections were imaged at 60X magnification using confocal microscopy. (Fig. 2.B) To isolate pure populations from collagenase dispersed tissues, the epithelial and hematopoietic cell fractions were sequentially removed by negative selection with magnetic beads. The remaining cells were stained with P1H12 and ECs were isolated by positive selection with magnetic beads. (Fig. 2.C) RT-PCR analysis used to assess the purity of the EC preparations. Semiquantitative PCR analysis was performed on cDNA generated either directly from colorectal cancer tissue (unfractionated tumor) or from purified ECs isolated from normal colonic mucosa (normal EC fraction) or colorectal cancer (tumor EC fraction). PCR amplification of the epithelial specific marker cytokeratin 20 (CK20), demonstrated its expression was limited to the unfractionated tumor. Two endothelial specific markers, vWF and VE-cadherin (VE-Cad) showed robust amplification only in the endothelial fractions, validating the purity and enrichment protocol shown in (Fig. 2.B). The ubiquitous housekeeping enzyme GAPDH was observed in all samples.

No signal was detected in the no-template (NT) control. cDNA templates were diluted 1:10, 1:100, 1:1000, 1:4000, and 1:40,000 as indicated by the declining wedge. (Fig. 2.D) The relative expression level of select genes was determined by measuring the tag abundance from several SAGE libraries combined into four groups. The first was composed of ~193,000 tags from the two in vivo-derived EC preparations (Endothelial Cell Fraction) while the second contained a single library of ~57,000 tags containing macrophages and other leukocytes derived from the negative selection (Hematopoietic Fraction). The fourth library contained ~401,000 tags from cultured HUVEC and HMVEC (Endothelial Cells in Culture), and the fourth consisted of ~748,000 tags from 6 colon cancer cell lines in culture (Epithelial Cells). After normalization, the library with the highest tag number for each marker was given a value of 100%, and the corresponding relative expression levels of the remaining 3 libraries was plotted on the ordinate. Note the high level of CD31 present on hematopoietic cells, the likely cause of the impurity of the initial endothelial selection, compared with the selectivity of P1H12.

[49] Fig. 3A- 3E). Expression of Pan-Endothelial Markers (PEMs) is limited to ECs. The endothelial origin of PEMs identified by SAGE was confirmed using a highly sensitive in situ hybridization assay. Localization of novel PEMs to the ECs was demonstrated by examining two representative PEMs, PEM3 (Fig. 3A) and PEM6 (Fig. 3B) in lung cancer and colon cancer, respectively. Hevin expression was readily detected in the ECs of a colon tumor (Fig. 3C) despite its low level of expression in cultured ECs. Expression of VEGFR2 was readily detectable in the ECs of both normal (Fig. 3D) and malignant colon tissue (Fig. 3E).

[50] Fig. 4A-4J. Expression of Tumor Endothelial Markers (TEMs). (Fig. 4A) RT-PCR analysis confirmed the tumor specific expression of selected novel TEMs. Semiquantitative PCR analysis was performed on cDNA generated either from purified epithelial cells as a negative control (Control) or from purified ECs isolated from normal colonic mucosa (Normal ECs) or

colorectal cancer (Tumor ECs) from two different patients. Two endothelial specific markers, vWF and PEM6 showed robust amplification only in the endothelial fractions whereas the ubiquitous housekeeping enzyme GAPDH was observed in all samples. TEM1 (BSC-TEM1), TEM 17 (BSC-TEM7) and TEM22 (BSC-TEM9) were specifically expressed in tumor compared to normal ECs. The cDNA template was diluted 1:10, 1:100, 1:1000, and 1:10,000 as indicated by the declining wedge. (Fig. 4 B- 4J) The endothelial origin of TEMs identified by SAGE was confirmed using in situ hybridization as in Fig 3. Expression of TEM 1 (BSC-TEM1) (Fig. 4 B) and TEM17 (BSC-TEM7) (Fig. 4 C) was demonstrated to be highly specific to the ECs in colorectal cancers; sections were imaged in the absence of a counterstain to show the complete lack of detectable expression in the non-endothelial cells of the tumor. Expression of TEM17 (BSC-TEM7) in ECs was demonstrated in a metastatic liver lesion from a primary colorectal cancer (Fig. 4 D), a lung (Fig. 4 E), breast (Fig. 4 F), pancreatic (Fig. 4 G) and brain cancer (Fig. 4 H), as well as in a sarcoma (Fig. 4 I). TEM 17 (BSC-TEM7) was also localized to vessels during normal physiological angiogenesis of the corpus luteum (Fig. 4 J).

DETAILED DESCRIPTION OF THE INVENTION

[51] We identified 46 human genes that were expressed at significantly higher levels (> 10-fold) in tumor endothelium than in normal endothelium, and 33 genes that were expressed at significantly lower levels in human tumor versus normal endothelium. See Tables 2 and 4, respectively. Most of these genes were either not expressed or expressed at relatively low levels in Endothelial Cells (ECs) maintained in culture. Moreover, we identified 93 genes which are expressed in both normal and tumor human endothelium. Interestingly, the tumor endothelium genes were expressed in all tumors tested, regardless of its tissue or organ source. Most tumor endothelium genes were also expressed in corpus luteum and wounds.

[52] As the work has progressed, we have refined and classified our original 46 tumor endothelial markers. We have named these markers TEMs and renumbered them consecutively by the prevalence of their tags in our SAGE analysis. Originally we had not used a consecutive numbering system. Our non-consecutive numbering system has been renamed as BSC-TEMs. For most of the original 46 SAGE Tags, we now provide full-length nucleic acid and protein sequence. In some cases, the sequences were obtained through the public databases, in others the sequences were obtained by cloning and through the use of gene prediction tools. In some cases, we found SAGE Tags corresponding to genes having different splice varients or with known polymorphisms. For example, in one case the SAGE Tag BSC-TEM3 has been found to hybridize to an alternatively spliced form of the transcript encoding BSC-TEM7. The proteins encoded by the two transcripts are the same; therefore they are cumulatively called TEM7. A highly related sequence was found via homology searches, BSC-TEM7R. This paralog sequence is now called TEM3. See Table 2, which follows, showing tumor endothelial markers by order of prevalence (except for TEM 3). Column 1 indicates the prevalence number. Column 2 indicates the original nomenclature. Column 3 indicates the short tags. Column 4 indicates the long tags. Column 5 indicates the accession number in GenBank. Column 6 indicates the sequence identifiers for the short tag, the long tag, the full nucleic acid, and the protein. Column 7 provides a functional description, which is expanded below in the text.

TEM1	BSC-TEM1	GGGGCTGCCCA	GGGGCTGCCCAGCTGA	NM020404	SEQ ID NO: 94, 309, 195, 196	tumor endothelial marker 1 precursor
TEM 2	BSC-TEM2	GATCTCCGTGT			SEQ ID NO: 95, 197.198	sapiens tumor endothelial marker 2 (BSC-TEM2) mRNA/mouse Ras, dexamethasone-induced 1 (RASD1), mRNA
TEM 3	BSC-TEM7R				SEQ ID NO:199, 200	human ortholog of mouse paralog of mouse TEM-7
TEM 4		CTTTCTTTGAG	CTTTCTTTGAGTTTTAA	AB034203	SEQ ID NO:97, 311, 201, 202	Homo sapiens dickkopf-3 (DKK-3) mRNA,
TEM 5	BSC-TEM4	TATTAACTCTC	TATTAACTCTCTTTGGA		SEQ ID NO:98, 312, 203, 204	Tumor endothelial marker 4
TEM 6		CAGGAGACCCC	CAGGAGACCCCAGGCCC	X57766	SEQ ID NO:99, 314, 205, 206	Human stromelysin-3 mRNA.
TEM 7		GGAAATGTCAA	GGAAATGTCAGCAAGTA	BC002576	SEQ ID NO:100, 315.207, 208	matrix metalloproteinase 2 (gelatinase A, 72kD gelatinase, 72kD type IV collagenase)

TEM 8		CCTGGTTCAGT			SEQ ID NO:101, 316, 209, 210	HeyL transcription factor
TEM 9	BSC-TEM5	TTTTTAAGAAC	TTTTTAAGAACTCGGGT		SEQ ID NO:102, 317, 211, 212	
TEM 10		TTTGGTTTTCC	TTTGGTTTTCCAAAAGA	J03464, M18057, X02488	SEQ ID NO:103, 319, 213, 214	Human collagen alpha-2 type I mRNA, complete cds, clone pHCOL2A1.
TEM 11		ATTTTGTATGA	ATTTTGTATGATTTTTA	NM_002508	SEQ ID NO:104, 321, 215, 216	nidogen/entactin
TEM 12		ACTTTAGATGG	ACTTTAGATGGGAAGCC	X52022	SEQ ID NO:105, 322, 217, 218	H.sapiens RNA for type VI collagen alpha3 chain.
TEM 13		GAGTGAGACCC	GAGTGAGACCCAGGAGC	M11749	SEQ ID NO:106, 324, 219, 220	Human Thy-1 glycoprotein gene, complete cds.
TEM 14		GTACACACACC	GTACACACACCCCCACC		SEQ ID NO:107, 325, 221, 223	Cystatin SN

TEM 14		GTACACACACC	GTACACACACCCCCACC	X54667	SEQ ID NO:107, 325, 222, 224	H.sapiens mRNA for cystatin S.
TEM 15		CCACAGGGGAT	CCACAGGGGATTCTCCT	NM_000090	SEQ ID NO:108, 327, 225, 226	Human mRNA 3' region for pro-alpha1(III) collagen.
TEM 16	BSC-TEM6	TTAAAAGTCAC	TTAAAAGTCACTGTGCA		SEQ ID NO:109, 328, 227, 228	
TEM 17	BSC-TEM7	ACAGACTGTTA	ACAGACTGTTAGCCAAG	AF279144	SEQ ID NO:110, 329, 229, 230	Human Tumor endothelial marker 7
TEM 18		CCACTGCAACC			SEQ ID NO:111	
TEM 19	BSC-TEM8	CTATAGGAGAC			SEQ ID NO:112, 330, 231, 232	
TEM 20		GTTCCACAGAA		NM_000089	SEQ ID NO:113, 233, 234	collagen, type I, alpha 2 (COL1A2

TEM 21		TACCACCTCCC	TACCACCTCCCTTTCCT		SEQ ID NO:114, 331, 235, 236	Homo sapiens mRNA; cDNA DKFZp762B245 (from clone DKFZp762B245);
TEM 22	BSC-TEM9	GCCCTTTCTCT	GCCCTTTCTCTGTAGTT	NM_006039	SEQ ID NO:115, 334, 237, 238	endocytic receptor (macrophage mannose receptor family) (KIAA0709),
TEM 23		TTAAATAGCAC	TTAAATAGCACCTTTAG		SEQ ID NO:116, 335	no match
TEM 24		AGACATACTGA	AGACATACTGACAGAAT	NM_022648	SEQ ID NO:117, 336, 239, 240	Homo sapiens mRNA; cDNA DKFZp434G162 (from clone DKFZp434G162);
TEM 25		TCCCCCAGGAG	TCCCCCAGGAGCCACCG	L35279, NM_006129	SEQ ID NO:118, 338, 241, 242	Homo sapiens (clone KT2) bone morphogenetic protein-1 (BMP-1) mRNA
TEM 26		AGCCCAAAGTG			SEQ ID NO:119	No Match
TEM 27		ACTACCATAAC		NM_003062	SEQ ID NO:120, 243.244	Homo sapiens mRNA for MEGF5, partial cds.
TEM 28		TACAAATCGTT	TACAAATCGTTGTCAAA	NM_014859	SEQ ID NO:121, 339, 245, 246	Homo sapiens mRNA for KIAA0672 protein, complete cds.

TEM 29		TTGGGTGAAAA			SEQ ID NO:122, 247, 248	ESTs (2 unigene clusters)
TEM 30		CATTATCCAAA	CATTATCCAAAAACAAT	THC534029, X68742, AI262158, AI88747, AI394565, AA679721	SEQ ID NO:123, 340, 249, 250	integrin, alpha 1
TEM 31		AGAAACCACGG	AGAAACCACGGAAATGG	NM_001845	SEQ ID NO:124, 341, 251, 252	hypothetical protein KIAA1164
TEM 32		ACCAAAACCAC			SEQ ID NO:125	no match
TEM 33		TGAAATAAAC		NM_000255	SEQ ID NO:126, 253, 254	methylmalonyl Coenzyme A mutase
TEM 34		TTTGGTTTCC			SEQ ID NO:127	no match
TEM 35		GTGGAGACGGA	GTGGAGACGGACTCTGT	ESTAI186535	SEQ ID NO:128, 345, 255, 358	est

TEM 36		TTTGTGTTGTA	TTTGTGTTGTATATTTA	NM_004370	SEQ ID NO:129, 346, 256, 257	est
TEM 37		TTATGTTTAAT	TTATGTTTAATAGTTGA	NM_002345	SEQ ID NO:130, 347, 258, 259	Human lumican mRNA, complete cds.
TEM 38		TGGAAATGAC	TGGAAATGACCCAAAAA	NM_000088	SEQ ID NO:131, 348, 260, 261	collagen type1 alpha1
TEM 39		TGCCACACAGT	TGCCACACAGTGACTTG	NM_003239	SEQ ID NO:132, 350, 262, 263	Human transforming growth factor-beta 3 (TGF-beta3) mRNA, complete
TEM 40		GATGAGGAGAC	GATGAGGAGACTGGCAA		SEQ ID NO:133, 351, 264, 265	collagen, type I, alpha 2
TEM 41		ATCAAAGGTTT	ATCAAAGGTTTGATTTA		SEQ ID NO:134, 352, 266, 267	est
TEM 42		AGTCACTAGT	AGTCACATAGTACATAA	NM_025226	SEQ ID NO: 135, 353, 268, 269	ESTs

TEM 43		TTCGGTTGG TC	TTCGGTTGGTCAAA GAT		SEQ ID NO:136, 354	No match
TEM 44		CCCCACACG GG	CCCCACACGGGCAA GCA	NM_01835 4v	SEQ ID NO: 137, 355, 270, 271	Homo sapiens cDNA FLJ11190 fis, clone PLACE1007583.
TEM 45		GGCTTGCCT TT	GGCTTGCCTTTTTGT AT	NM_00036 6	SEQ ID NO:138, 356, 272, 273	est
TEM 46		ATCCCTTCCC G	ATCCCTTCCCGCCA CAC	NM_00268 8	SEQ ID NO:139, 357, 274, 275	Homo sapiens mRNA for peanut-like protein 1, PNUTL1 (hCDCrel-1).

[53] The studies described below provide the first definitive molecular characterization of ECs in an unbiased and general manner. They lead to several important conclusions that have direct bearing on long-standing hypotheses about angiogenesis. First, it is clear that normal and tumor endothelium are highly related, sharing many endothelial cell specific markers. Second, it is equally clear that the endothelium derived from tumors is qualitatively different from that derived from normal tissues of the same type and is also different from primary endothelial cultures. Third, these genes are characteristically expressed in tumors derived from several different tissue types, documenting that tumor endothelium, in general, is different from normal endothelium. Fourth, the genes expressed differentially in tumor endothelium are also expressed during other angiogenic processes such as corpus luteum formation and wound healing. It is therefore more appropriate to regard the formation of new vessels in tumors as "neoangiogenesis" rather than "tumor angiogenesis" *per se*. This distinction is important from a variety of perspectives, and is consistent with the idea that tumors recruit vasculature using much of, or basically the same signals elaborated during other physiologic or pathological processes. That tumors represent "unhealed wounds" is one of the oldest ideas in cancer biology.

[54] The nature and precise biological function of many of the Tumor Endothelial Markers (TEMs) identified here are unknown. Of the previously characterized genes shown in Table 2, it is intriguing that several encode proteins involved in extracellular matrix formation or remodelling (TEM 6, TEM 6, TEM 10, TEM 7, TEM 11, TEM 12, TEM 14, TEM 20, TEM 24, TEM 25, TEM 27, TEM 37, TEM 38, and TEM 40,) Deposition of extracellular matrix is likely critical to the growth of new vessels. Finally, it is perhaps not surprising that so many of the endothelial-specific transcripts identified here, whether expressed only in neovasculature or in endothelium in general, have not been previously characterized, and some are not even represented in EST databases. In part, this may be due to the fact that the EST databases are heavily biased toward certain

tissues, but moreover, may be due to the fact that even in highly vascularized tissues endothelial cells are still a relatively small proportion of the population. Thus, the sensitivity of the SAGE method is a particularly appropriate tool.

[55] Sequence and literature study has permitted the following identifications to be made among the family of TEM proteins. TEM proteins have been identified which contain transmembrane regions. These include TEM 1, TEM 3, TEM 9, TEM 13, TEM 17, TEM 19, TEM 22, TEM 30, and TEM 44. TEM proteins have been identified which are secreted proteins, including TEM 4, TEM 6, TEM 7, TEM 10, TEM 12, TEM 14, TEM 20, TEM 25, TEM 27, TEM 31, TEM 36, TEM 37, TEM 38, and TEM 39. HeyL (TEM 8) is a transcription factor which may be involved in regulating TEMs as one or more groups. The protein corresponding to the tag for TEM44 was found in the public databases, but no biological function has yet been ascribed to it.

[56] TEM 1 has been named endosialin in the literature. It has a signal sequence at amino acids 1-17 and a transmembrare domain at amino acids 686-708. Thus it is a cell surface protein. Its extracellular domain is at resiudes 1-685. Endosialin may be involved in endocytosis. The mouse ortholog is predicte d to have a signal peptide at residues 1-21.

[57] TEM 2 is a dexamethasone induced, ras related protein homolog of 266 amino acids. It has neither a signal sequence nor a transmembrane domain. Thus it is neither a cell surface nor a secreted protein. TEM 2 plays a role in signal transduction. It regulates alterations in cell morphology, proliferation, and cell-extracellular matrix interactions.

[58] TEM 3 (originally termed TEM 7R) has both a signal sequence (at residues 1-24 or 1-30) and a transmembrane domain (at residues 456 – 477). Thus it is a cell surface protein. The portion of the protein which is extracelular is at amino acids 1- 455. TEM 3 has domains with homology to integrins, plexin,

and adhesion molecules. TEM 3 may regulate GTPases that control signal transduction pathways linking plasma membrane receptors to the actin cytoskeleton. In the mouse ortholog, the signal peptide is predicted to be residues 1-30.

[59] TEM 4 is also known as DKK –3. It has a signal sequence (residues1-16), suggesting that is a secreted protein. TEM 4 regulates *wnt* signaling, and it may be involved in vasculogenesis and *wnt*-dependent signaling for endothelial growth. TEM 4 is an inhibitor of Wnt oncogene and such *inhibition* can be determined by assay. Tsuji et al., Biochem.Biophys.Res.Comm. 268:20-4, 2000.

[60] TEM 5 appears to be neither secreted nor a cell surface protein. TEM 5 appears to be a component of a G protein - GTPase signaling pathway.

[61] TEM 6 is also known as stromelysin - 3 /Matrix metalloproteinase 11 (MMP -11). It has a signal sequence at residues 1-31, but no transmembrane domain. It has an alternative signal peptide splice site at residues 108-109. Thus it appears to be a secreted protein. TEM 6 belongs to the zinc metaloprotease family, also known *as the matrixin* subfamily. TEM 6 is expressed in most invasive carcinomas. Alpha 1 - protease inhibitor is a natural substrate of MMP 11. TEM 6 degrades extracellhular matrix proteins such as collagen and is involved in extracellular matrix remodeling and cell migration. Stromelysin can be assayed using a casein-resorufin substrate, for example. See Tortorella and Arner, Inflammation Research 46 Supp. 2:S122-3, 1997.

[62] TEM 7 is a protein of many names, also being known as matrix metalloproeinase 2, gelatinase A, and 72KD type IV collagenase. TEM 7 has a signal sequence at residues 1- 26 and is a secreted protein. Like TEM 6, TEM 7 belongs to the matrixin subfamily (zinc metalloproteinases). TEM 7 cleaves gelatin type I, collagen type I, IV, V VII and X.. TEM 7 associates with integrin on the surface of endothelial cells and promotes vascular invasion. TEM 7 is

involved in tissue remodeling. TEM 7 can be assayed using zymography or quenched fluorescent substrate hydrolysis, for example. Garbett, et al., Molecular Pathology 53:99-106, 2000. A fluorogenic matrix metalloproteinase substrae assay can also be used which employs methoxycoumarin continaing septapeptide analog of the alpha2(I) collagen cleavage site. See Bhide et al., J. Periodontology 71:690-700, 2000.

[63] TEM 8 is HEYL protein . It has neither a signal sequence nor a transmembrane domain. It is related to the hairy/Enhancer of split genes. TEM 8 is likely a nuclear protein, having a role as a transcription factor. TEM 8 belongs to a new class of Notch signal tranducers and plays a key role in various developmental processes, such as vascular development, somatogenesis and neurogenesis. SNP's at residues 615 and 2201 have Cytosine bases. Notch 3 mutations underlie the CADASIL vascular disorder. See *Mech Dev* 2000 Nov; 98 (1-2):175

[64] TEM 9 is a G- protein coupled receptor homolog, having both a signal sequence at residues 1-26 and 7 transmembrane domains. Thus it is a cell surface protein. Its extracellular region resides in amino acids 1-769. Its transmembrane domains are at residues 817-829 (TM2 and TM3), residues 899-929 (TM4 and TM5), and residues 1034-1040 (TM6 and TM7). TEM 9 acts as a G-protein coupled receptor with extracellular domains characteristic of cell adhesion proteins. One of its splice variants may function as a soluble receptor. TEM 9 may regulate cell polarity and cell migration. It may be involved in exocytosis based on latrophilin function. The mouse ortholog has a predicted signal peptide at residues 1-29.

[65] TEM 10 is collagen type I, alpha2 (COL1A2), which has a signal sequence at residues 1-22. It is an extracellular matrix (ECM) protein which is secreted subsequent to synthesis. TEM 10 interacts with a number of proteins including other ECM proteins, certain growth factors, and matrix metalloproteases. TEM

10 is required for the induction of endothelial tube formation and is involved in tissue remodeling. A variant at nucleotide 3233 which substitutes an A, is associated with osteogenesis imperfecta type IV. A variant at nucleotide 4321 substituting an A retains a wild type phenotype. Nucleotide 715 is a site of a polymorphism. Nucleotides 695-748 are deleted in Ehlers-Danos syndrome. Other mutations are associated with idiopathic osteoporosis, and atypical Marfan syndrome. Variants are known at nucleotides 226(T,C), 314(A,C), 385(T,C), 868 (G,A), 907(C,T), 965(A,G), 970(T,A), 1784 (G,C), 2017(T,G), 2172(C,A), 2284(T,C), 2308(T,C), 2323(T,G), 2344(T,G), 2604(G,A), 2974(A,T), 2903(A,G), 2995(C,T), 3274(C,T), 3581(A,C), 3991(A,C), 4201(G,T), 4434(C,T), 4551(A,C), 4606(C,A), 4947(T,C), 4978(C,T), 4982(G,T), 5051(G,T). PolyA sites are located at nucleotides 4450, 4550, 4885, and 5082. PolyA signals are located at 4420-4424, 4515-4520, 4529-4534, 4866-4871, 5032-5037, 5053-5058. TEM 10, 20, and 40 derive from the same gene but are different isoforms having different lengths.

[66] TEM 11 is Nidogen /Entactin. It is a secreted protein which has a signal sequence at residues 1-28. TEM 11 is an extracellular matrix protein which is a component of a basement membrane. TEM 11 binds to laminin and collagen IV and other extracellular matrix proteins. TEM 11 regulates capillary formation and is involved in tissue remodelling. Variations have been observed at nucleotides 4265(T,C), 4267(G,C,T), and 4738(T,G). Nidogen can be assayed by its effect on the morphology of astrocytes. See Grimpe et al., GLIA 28:138-49, 1999.

[67] TEM 12 is the alpha 3 chain of collagen type VI. It has a signal sequence at residues 1-25. A secreted protein, TEM 12 is an extrallcellular matrix protein. TEM 12 has a splice variant. TEM 12 is a major constituent of vascular subendothelium and is involved in tissue remodeling. It regulates platelet activation and aggregation. Alternatively spliced domains are located at nucleotides 347-964, 965-1567, 2153-3752, and 4541-5041.

[68] TEM 13 is also known as Thy -1 glycoprotein. It has both a signal sequence (at residues 1-19) and a transmembrane domain (at residues 143-159). Residues 131-161 are removed in a matured form of the protein. The extracellular region of the protein is resudes 1- 142 or residues 1-130. TEM 13 has a glycosyl phosphatidylinositol (GPI) anchor at residue 130 anchoring it to the membrane. TEM 13 is detectale in its soluble form in human serum. TEM 13 is reported to be a marker for activated endothelial cells (a marker of adult but not embryonic angiogenesis). TEM 13 on vascular endothelial cells may function as a possible vascular permeability modulator. Antibody to Thy-1 is a mitogenic signal for the CD4+CD45+ and CD8+CD45+ cells, but fails to induce proliferation in the CD45- T cells. Pingel et al., International Immunology 6:169-78, 1994. Thy-1 can be assayed as an inhibitor of such signal.

[69] TEM 14 is also known as cystatin S. It is a secreted protein with a signal sequence at residues 1-20 and an extracelllular region at residues 1-141. It is a cysteine protease inhibitor. TEM 14 may regulate cysteine protease function involved in angiogenesis and tissue remodeling. TEM14 is an inhibitor of the activity of papain and such inhibition can be assayed. Hiltke et al., J. Dental Research 78:1401-9, 1999.

[70] TEM 15 is collagen type III, alpha 1 (COL3A1). It has a signal sequence (residues 1-23) and is secreted. Type III collagen binds to von Willebrand factor. It is involved in cell-cell adhesion, proliferation, and migration activities. Variants at nucloetides 2104(C,A), 2194(G,A), 2346(C,T), 2740(C,T), 3157(T), 3468(G), 3652(T), 3666(C), 3693(C), 3755(G), 3756(T), 3824(C), 4546(A, G), 4661(G), 4591(C,T), 4665(C), 5292(C), 5293(C), and 5451 (A) have been observed.

[71] TEM 16 is a tensin homolog which is apparently an intracellular protein. It may have splice variants or isoforms. One form with 1704 amino acids has a region at the N-terminal domain which is similar to a tumor suppressor protein,

phosphatase and tensin homolog (PTEN). Tensin is a focal adhesion molecule that binds to actins and phosphorylated proteins. It is involved in cell migration linking signal tranduction pathways to the cytoskeleton. PTEN regulates tumor induced angiogenesis.

[72] TEM 17 (BSC-TEM 7) has a signal sequence which includes residues 1-18 and a transmembrane domain at residues 427-445. It is a cell surface marker with an extracellular region comprising residues 1-426. It has homologs in both mouse and *C. elegans*. Residues 137-244 share weak homology with nidogen; residues 280-344 share homology to PSI domains found in plexin, semaphorins and integrin beta subunits. Variants have been observed at nucleotides 1893(A,G), 1950(C,G), 2042(A,G), and 2220(G,A). In mouse TEM 17 the signal sequence includes residues 1-19.

[73] TEM 19 was originally reported to be tumor endothelial marker 8, *i.e.*, BSC-TEM 8. It has a signal sequence at residues 1-27 and a transmembrane domain at residues 322-343. It is a cell surface protein having an extracellular region at residues 1-321.TEM 19 has a von Willebrand Factor (vWF) A domain at residues 44-216; a domain at residues 34-253 which is found in leukointegrin alpha D chain; and a domain at residues 408-560 found in PRAM-1 or adaptor molecule –1 of the vinculin family. TEM 19's function is adhesion related. vonWillibrand Factor domains are typically involved in a variety of functions including vascular processes. TEM 19 may play a role in the migration of vascular endothelial cells. The mouse ortholog has a predicted signal peptide at residues 1-27.

[74] TEM 20 is collagen type I, alpha 2 (COL1A2). It has a signal sequence at residues 1-22 and is a secreted extracellular matrix protein. TEM 20 induces endothelial tube formation *in vitro* and is involved in tissue remodeling. Variants have been observed at nucleotides 226(T,C), 314(A,C), 385(T,C), 868 (G,A), 907(C,T), 965(A,G), 970(T,A), 1784(G,C), 2017(T,G), 2172(C,A), 2284(T,C),

2308(T,C), 2323(T,G), 2344(T,G), 2604(G,A), 2794(A,T), 2903(A,G), 2995(C,T), 3274(C,T), 3581(A,C), 3991(A,C), 4201(G,T), 4434(C,T), 4551(A,C), 4606(C,A), 4895-4901(–, GGACAAC), 4947(T,C), 4978(C,T), 4982(G,T), 5051(G,T).

[75] TEM 21 is a Formin – like protein homolog which is an intracellular protein. Formin related proteins interact with Rho family small GTPases, profilin, and other actin associated proteins. Formin-binding proteins bind to FH1 domains with their WW domains. TEM 21 has a proline rich FH1 domain at residues 221-449. Formin related proteins play crucial roles in morphogenesis, cell polarity , cytokinesis and reorganization of the actin cytoskeleton. They may also regulate apoptosis, cell adhesion and migration.

[76] TEM 22 is an endocytic receptor in the macrophage mannose receptor family. It has both a signal sequence at residues 1-30 and a transmembrane domain at residues 1415-1435, and resides on the cell surface. Its extracellular domain is amino acids 1- 1414. TEM 22 may be present as a soluble (secreted) form and act as an inhibitor. It may bind secreted phopholipase A2 (sPLA2) and mediate biological responses elicited by sPLA2. TEM 22 may have endocytic properties for sPLA2 and mediate endocytosis for endothelial related proteins. It may promote cell adhesion and be involved in cell-cell communication. Variations have been observed at nucleotide 5389 (A, G). TEM 22 mediates uptake of micro-organisms and host-derived glycoproteins. Groger et al., J. Immunology 165:5428-34, 2000.

[77] TEM 24 is tensin, an intracellular protein. It is a focal adhesion molecule that binds to actin filaments and interacts with phosphotyrosine containing proteins. It may mediate kinase signaling activities and regulate cellular transformation. Variations have been observed at nucleotides 2502 (A, G), 2622(A, G), 6027(A, G). TEM24 binds to actin filaments and interacts with phosphotyrosine-containing proteins. Chen et al., Biochem. J. 351 Pt2:403-11,

2000. TEM24 also binds to phosphoinositide3-kinase. Auger et al., J. Bio. Chem. 271:23452-7, 1996 TEM 24 also binds to nuclear protein p130. Lo et al., Bioessays 16:817-23, 1994.

[78] TEM 25 is Bone morphogenic protein 1 (BMP-1) which has a signal sequence at residues 1-22. It is a secreted protein. There are at least 6 isoforms of BMP-1 as well as splice variants which add carboxy terminal CUB domains and an additional EGF domain. TEM 25 is a metalloprotease enzyme. It cleaves the C-terminal propeptide of collagen type I, II and III and laminin 5 gamma 2 , proteins that are important for vascular processes. It is involved in cartilage formation. Variations have been observed at nucleotides 3106(C,T), 3248(G,A), 3369(G,A). TEM 25 cleave probiglycan at a single site, removing the propeptide and producing a biglycan molecule with an NH(2) terminus identical to that of the mature form found in tissues. Sctt et al., J. Biol. Chem. 275:30504-11, 2000. Laminin alpha 3 and gamma2 short chains are substraates of TEM 25. Amano et al., J. Biol. Chem. 275:22728-35, 2000.

[79] TEM 27 is known as Slit homolog 3, a secreted protein with a signal sequence at residues 1-27. TEM 27 is a secreted guide protein involved in migration, repulsion and patterning. It interacts with "round about" receptors (Robo receptors). TEM 27 may interact with extracellular matrix (ECM) proteins and is involved in cell adhesion. Variations have been observed at nucleotides 4772 (C,T)

[80] TEM 28 is similar to mouse nadrin (neuron specific GTPase activiating protein). TEM 28 is an intracellular protein with a RhoGAP domain. The RhoGAP domain activates RhoA, Rac1, and Cdc42 GTPases. It is involved in the reorganization of actin filaments and enhancing exocytosis. It may also be involved in cell signalling. Variations have been observed at nucleotide 3969 (A,C),

[81] TEM 29 is protein tyrosine phosphatase type IVA, member 3, isoform 1, an intracellular protein. It has alternate splice variants. TEM 29 belongs to a small class of prenylated protein tyrosine phosphatases (PTPs). It may be membrane associated by prenylation. PTPs are cell signaling molecules and play regulatory roles in a variety of cellular processes and promote cell proliferation. PTP PRL-3 regulates angiotensin –II induced signaling events.

[82] TEM 30 is integrin alpha 1, a cell surface protein having both a signal sequence (residues 1-28) and a transmembrane domain (residues 1142-1164). Its extracellular region includes amino acids 1-1141. TEM 30 is a receptor for laminin and collagen. It mediates a variety of adhesive interactions. TEM 30 is abundantly expressed on microvascular endothelial cells. It stimulates endothelial cell proliferation and vascularization. TEM 30 may regulate angiostatin production. Variations have been observed at nucleotide 418 (C,T). TEM 30 activates the Ras/Shc/mitogen-activated protein kinase pathway promoting fibroblast cell proliferation. It also acts to inhibit collagen and metalloproteinase synthesis. Pozzi et al., Proc. Nat. Acad. Sci. USA 97:2202-7, 2000,

[83] TEM 31 is Collagen IV alpha 1 (COL4A1) a secreted protein with a at residues 1-27. TEM 31 is a component of the basement membrane. It binds to alpha3 beta 1integrin and promotes integrin mediated cell adhesion. Non-collagenous domains of type IV subunits are involved in tumoral angiogenesis. TEM 31 is involved in tissue remodeling. Variations have been observed at nucleotide 4470 (C,T)

[84] TEM 33 is methylmalonyl Co-A Mutase a protein which is localized in the mitochondrial matrix. It degrades several amino acids, odd-numbered-acid fatty acids, and cholesterol to the tricarboylic acid cycle. A defect in TEM 33 causes a fatal disorder in organic acid metabolism termed methylmalonic acidurea. Variations have been observed at nucleotides 1531(G,A), 1671(G,A), 2028(T,C), 2087(G,A), 2359(A,G), 2437(C,A), 2643(G,C), 2702(G,C). TEM 33

converts L-methylmalonyl CoA to succinyl CoA. This reaction can be assayed as is known in the art. See, e.g., Clin. Chem. 41(8 Pt I):1164-70, 1995.

[85] TEM 36 is collagen type XII, alpha1 (COL12A1), an extracellular matrix protein having a signal sequence at residues 1-23 or 24. TEM 36 has von Willebrand Factor (vWF) type A domains, Fibronectin type III domains, and thrombospondin N-terminal like domain. TEM 36 is expressed in response to stress environment. TEM 36 may organize extracellular matrix architecture and be involved in matrix remodeling. There are two isoforms of the protein, a long form and a short form. The short form is missing amino acids 25-1188, and therefore nucleotides 73 to 3564. Both forms share the signal sequence and are therefore both secreted.

[86] TEM 37 is lumican, an extracellular matrix sulfated proteoglycan having a signal sequence at residues 1-18. Lumican interacts with proteins that are involved in matrix assembly such as collagen type I and type VI; it is involved in cell proliferation and tissue morphogenesis. Lumican plays an important role in the regulation of collagen fiber assembly. Variations have been observed at nucleotides 1021(G,T), 1035(A,G), 1209(A,G), 1259(A,C), 1418(C,A), 1519(T,A). TEM 37 is a binding partner of TGF-β. See FASEB J. 15:559-61, 2000. One assay that can be used to determine TEM 37 activity is a collagen fibril formation/sedimentation assay. Svensson et al., FEBS Letters 470:178-82, 2000.

[87] TEM 38 is collagen type I, alpha 1 (COL1A1), an extracellular matrix protein having a signal sequence at residues 1-22. Type I collagen promotes endothelial cell migration and vascularization and induces tube formation and is involved in tissue remodelling. Telopeptide derivative is used as a marker for malignancy and invasion for certain cancer types. Variations have been observed at nucleotides 296(T,G), 1810(G,A), 1890(G,A), 2204(T,A), 3175(G,C), 3578(C,T), 4298(C,T), 4394(A,T), 4410(A,C), 4415(C.A), 4419 (A,T), 4528(C,A), 4572(G,T), 4602(T,C), 5529(T,C), 5670(C,T), 5985(C,T), 6012(C,T).

[88] TEM 39 is transforming growth factor β –3 (TGF-beta3). It has a signal sequence at residues 1-23. It is a secreted protein. TEM 39 regulates cell growth and differentiation. TGF-beta isoforms play a major role in vascular repair processes and remodeling. Variations have been observed at nucleotide 2020(G,T).

[89] TEM 41 is similar to Olfactomedin like protein. It appears to be an intracellular protein, having no obvious predicted signal sequence. Olfactomedin is the major glycoprotein of the extracellular mucous matrix of olfactory neuroepithelium. TEM 41 shares homology with latrophilin (extracellular regions) which has cell-adhesive type domains. TEM 41 may be involved in adhesive function.

[90] **TEM 42 is MSTP032 protein, a cell surface protein having a trasmembrane domain at residues 42-61. Its function is unknown and it shares little homology with other proteins. Variations have been observed at nucleotides 418(A,T), 724(C,A).**

[91] TEM 44 is a hypothetical protein FLJ11190 (NM_018354) which has two predicted transmembrane domains at residues 121-143 and 176 –1 97. Residues 144-175 may form an extracellular region. TEM 44's function is not known and shares no homology to other known proteins.

[92] TEM 45 is tropomyosin 1 (alpha), a protein which is intracellular. It forms dimers with a beta subunit. It influences actin function. TEM 45 may be involved in endothelial cell cytoskeletal rearrangement. Variations have been observed at nucleotides 509(A,C), 621(A,C), 635(T,G), 642(C,G), 1059(G,T).

[93] TEM 46 is peanut-like 1 protein/septin 5, which belongs to the septin family. Proteins in the septin family bind to GTP and phosphatidylinositol 4,5-bisphosphate. They are involved in the signal tranduction cascades controlling cytokinesis and cell division.

[94] NEM 4 is a member of the small inducible cytokine subfamily A (cys-cys), member 14 (SCYA14). NEM4 is a secreted protein characterized by two adjacent cysteine residues. One isoform lacks internal 16 amino acids compared to isoform 2.

[95] NEM 22 shares homology with guanylate kinase-interacting protein 1Maguin-1. It is a membrane associated protein.

[96] NEM 23 is human signaling lymphocytic acitavation molecule (SLAM). It has a signal sequence at residues 1-20. The extracellular domain may reside at residues 21-237. There is a secreted isoform of the protein.

[97] NEM33 is netrin 4. It induces neurite outgrowth and promotes vascular development. At higher concentration, neurite outgrowth is inhibited.

[98] ECs represent only a minor fraction of the total cells within normal or tumor tissues, and only those EC transcripts expressed at the highest levels would be expected to be represented in libraries constructed from unfractionated tissues. The genes described in the current study should therefore provide a valuable resource for basic and clinical studies of human angiogenesis in the future. Genes which have been identified as tumor endothelial markers (TEMs) correspond to tags shown in SEQ ID NOS: 94-139, 173-176, 180-186. Genes which have been identified as normal endothelial markers (NEMs) correspond to tags shown in SEQ ID NOS: 140-172. Genes which have been identified as pan-endothelial markers (PEMs) *i.e.,* expressed in both tumor and normal endothelial cells correspond to tags shown in SEQ ID NOS: 1-93. Genes which have been previously identified as being expressed predominantly in the endothelium correspond to PEM tags shown in SEQ ID NOS: 1-6, 8, 10-15. Markers in each class can be used interchangeably for some purposes.

[99] Isolated and purified nucleic acids, according to the present invention are those which are not linked to those genes to which they are linked in the human genome. Moreover, they are not present in a mixture such as a library containing a multitude of distinct sequences from distinct genes. They may be, however, linked to other genes such as vector sequences or sequences of other genes to which they are not naturally adjacent. Tags disclosed herein, because of the way that they were made, represent sequences which are 3' of the 3' most restriction enzyme recognition site for the tagging enzyme used to generate the SAGE tags. In this case, the tags are 3' of the most 3' most NlaIII site in the cDNA molecules corresponding to mRNA. Nucleic acids corresponding to tags may be RNA, cDNA, or genomic DNA, for example. Such corresponding nucleic acids can be determined by comparison to sequence databases to determine sequence identities. Sequence comparisons can be done using any available technique, such as BLAST, available from the National Library of Medicine, National Center for Biotechnology Information. Tags can also be used as hybridization probes to libraries of genomic or cDNA to identify the genes from which they derive. Thus, using sequence comparisons or cloning, or combinations of these methods, one skilled in the art can obtain full-length nucleic acid sequences. Genes corresponding to tags will contain the sequence of the tag at the 3' end of the coding sequence or of the 3' untranslated region (UTR), 3' of the 3' most recognition site in the cDNA for the restriction endonuclease which was used to make the tags. The nucleic acids may represent either the sense or the anti-sense strand. Nucleic acids and proteins althought disclosed herein with sequence particularity, may be derived from a single individual. Allelic variants which occur in the population of humans are including within the scope of such nucleic acids and proteins. Those of skill in the art are well able to identify allelic variants as being the same gene or protein Given a nucleic acid, one of ordinary skill in the art can readily determine an open reading frame present, and consequently the sequence of a polypeptide encoded by the open reading frame and, using techniques well known in the art, express such protein in a suitable

host. Proteins comprising such polypeptides can be the naturally occurring proteins, fusion proteins comprising exogenous sequences from other genes from humans or other species, epitope tagged polypeptides, etc. Isolated and purified proteins are not in a cell, and are separated from the normal cellular constituents, such as nucleic acids, lipids, etc. Typically the protein is purified to such an extent that it comprises the predominant species of protein in the composition, such as greater than 50, 60 70, 80, 90, or even 95% of the proteins present.

[100] Using the proteins according to the invention, one of ordinary skill in the art can readily generate antibodies which specifically bind to the proteins. Such antibodies can be monoclonal or polyclonal. They can be chimeric, humanized, or totally human. Any functional fragment or derivative of an antibody can be used including Fab, Fab', Fab2, Fab'2, and single chain variable regions. So long as the fragment or derivative retains specificity of binding for the endothelial marker protein it can be used. Antibodies can be tested for specificity of binding by comparing binding to appropriate antigen to binding to irrelevant antigen or antigen mixture under a given set of conditions. If the antibody binds to the appropriate antigen at least 2, 5, 7, and preferably 10 times more than to irrelevant antigen or antigen mixture then it is considered to be specific.

[101] Techniques for making such partially to fully human antibodies are known in the art and any such techniques can be used. According to one particularly preferred embodiment, fully human antibody sequences are made in a transgenic mouse which has been engineered to express human heavy and light chain antibody genes. Multiple strains of such transgenic mice have been made which can produce different classes of antibodies. B cells from transgenic mice which are producing a desirable antibody can be fused to make hybridoma cell lines for continuous production of the desired antibody. See for example, Nina D. Russel, Jose R. F. Corvalan, Michael L. Gallo, C. Geoffrey Davis, Liise-Anne Pirofski. Production of Protective Human Antipneumococcal Antibodies by Transgenic Mice with Human Immunoglobulin Loci *Infection and Immunity* April 2000, p.

1820-1826; Michael L. Gallo, Vladimir E. Ivanov, Aya Jakobovits, and C. Geoffrey Davis. The human immunoglobulin loci introduced into mice: V (D) and J gene segment usage similar to that of adult humans *European Journal of Immunology* 30: 534-540, 2000; Larry L. Green. Antibody engineering via genetic engineering of the mouse: XenoMouse strains are a vehicle for the facile generation of therapeutic human monoclonal antibodies *Journal of Immunological Methods 231* 11-23, 1999; Yang X-D, Corvalan JRF, Wang P, Roy CM-N and Davis CG. Fully Human Anti-interleukin-8 Monoclonal Antibodies: Potential Therapeutics for the Treatment of Inflammatory Disease States. *Journal of Leukocyte Biology* Vol. 66, pp401-410 (1999); Yang X-D, Jia X-C, Corvalan JRF, Wang P, CG Davis and Jakobovits A. Eradication of Established Tumors by a Fully Human Monoclonal Antibody to the Epidermal Growth Factor Receptor without Concomitant Chemotherapy. *Cancer Research* Vol. 59, Number 6, pp1236-1243 (1999) ; Jakobovits A. Production and selection of antigen-specific fully human monoclonal antibodies from mice engineered with human Ig loci. *Advanced Drug Delivery Reviews* Vol. 31, pp: 33-42 (1998); Green L and Jakobovits A. Regulation of B cell development by variable gene complexity in mice reconstituted with human immunoglobulin yeast artificial chromosomes. *J. Exp. Med.* Vol. 188, Number 3, pp: 483-495 (1998); Jakobovits A. The long-awaited magic bullets: therapeutic human monoclonal antibodies from transgenic mice. *Exp. Opin. Invest. Drugs* Vol. 7(4), pp : 607-614 (1998) ; Tsuda H, Maynard-Currie K, Reid L, Yoshida T, Edamura K, Maeda N, Smithies O, Jakobovits A. Inactivation of Mouse HPRT locus by a 203-bp retrotransposon insertion and a 55-kb gene-targeted deletion: establishment of new HPRT-Deficient mouse embryonic stem cell lines. *Genomics* Vol. 42, pp: 413-421 (1997) ; Sherman-Gold, R. Monoclonal Antibodies: The Evolution from '80s Magic Bullets To Mature, Mainstream Applications as Clinical Therapeutics. *Genetic Engineering* News Vol. 17, Number 14 (August 1997); Mendez M, Green L, Corvalan J, Jia X-C, Maynard-Currie C, Yang X-d, Gallo M, Louie D, Lee D, Erickson K, Luna J, Roy C, Abderrahim H, Kirschenbaum F, Noguchi M,

Smith D, Fukushima A, Hales J, Finer M, Davis C, Zsebo K, Jakobovits A. Functional transplant of megabase human immunoglobulin loci recapitulates human antibody response in mice. *Nature Genetics* Vol. 15, pp: 146-156 (1997); Jakobovits A. Mice engineered with human immunoglobulin YACs: A new technology for production of fully human antibodies for autoimmunity therapy. *Weir's Handbook of Experimental Immunology, The Integrated Immune System* Vol. IV, pp: 194.1-194.7 (1996) ; Jakobovits A. Production of fully human antibodies by transgenic mice. *Current Opinion in Biotechnology* Vol. 6, No. 5, pp: 561-566 (1995) ; Mendez M, Abderrahim H, Noguchi M, David N, Hardy M, Green L, Tsuda H, Yoast S, Maynard-Currie C, Garza D, Gemmill R, Jakobovits A, Klapholz S. Analysis of the structural integrity of YACs comprising human immunoglobulin genes in yeast and in embryonic stem cells. *Genomics* Vol. 26, pp: 294-307 (1995); Jakobovits A. YAC Vectors: Humanizing the mouse genome. *Current Biology* Vol. 4, No. 8, pp: 761-763 (1994); Arbones M, Ord D, Ley K, Ratech H, Maynard-Curry K, Otten G, Capon D, Tedder T. Lymphocyte homing and leukocyte rolling and migration are impaired in L-selectin-deficient mice. *Immunity* Vol. 1, No. 4, pp: 247-260 (1994); Green L, Hardy M, Maynard-Curry K, Tsuda H, Louie D, Mendez M, Abderrahim H, Noguchi M, Smith D, Zeng Y, et. al. Antigen-specific human monoclonal antibodies from mice engineered with human Ig heavy and light chain YACs. *Nature Genetics* Vol. 7, No. 1, pp: 13-21 (1994); Jakobovits A, Moore A, Green L, Vergara G, Maynard-Curry K, Austin H, Klapholz S. Germ-line transmission and expression of a human-derived yeast artificial chromosome. *Nature* Vol. 362, No. 6417, pp: 255-258 (1993) ; Jakobovits A, Vergara G, Kennedy J, Hales J, McGuinness R, Casentini-Borocz D, Brenner D, Otten G. Analysis of homozygous mutant chimeric mice: deletion of the immunoglobulin heavy-chain joining region blocks B-cell development and antibody production. *Proceedings of the National Academy of Sciences USA* Vol. 90, No. 6, pp: 2551-2555 (1993); Kucherlapati et al., U.S. 6,1075,181.

[102] Antibodies can also be made using phage display techniques. Such techniques can be used to isolate an initial antibody or to generate variants with altered specificity or avidity characteristics. Single chain Fv can also be used as is convenient. They can be made from vaccinated transgenic mice, if desired. Antibodies can be produced in cell culture, in phage, or in various animals, including but not limited to cows, rabbits, goats, mice, rats, hamsters, guinea pigs, sheep, dogs, cats, monkeys, chimpanzees, apes.

[103] Antibodies can be labeled with a detectable moiety such as a radioactive atom, a chromophore, a fluorophore, or the like. Such labeled antibodies can be used for diagnostic techniques, either *in vivo*, or in an isolated test sample. Antibodies can also be conjugated, for example, to a pharmaceutical agent, such as chemotherapeutic drug or a toxin. They can be linked to a cytokine, to a ligand, to another antibody. Suitable agents for coupling to antibodies to achieve an anti-tumor effect include cytokines, such as interleukin 2 (IL-2) and Tumor Necrosis *Factor* (TNF); photosensitizers, for use in photodynamic therapy, including aluminum (III) phthalocyanine tetrasulfonate, hematoporphyrin, and phthalocyanine; radionuclides, such as iodine-131 (^{131}I), yttrium-90 (^{90}Y), bismuth-212 (^{212}Bi), bismuth-213 (^{213}Bi), technetium-99m (^{99m}Tc), rhenium-186 (^{186}Re), and rhenium-188 (^{188}Re); antibiotics, such as doxorubicin, adriamycin, daunorubicin, methotrexate, daunomycin, neocarzinostatin, and carboplatin; bacterial, plant, and other toxins, such as diphtheria toxin, pseudomonas exotoxin A, staphylococcal enterotoxin A, abrin-A toxin, ricin A (deglycosylated ricin A and native ricin A), TGF-alpha toxin, cytotoxin from chinese cobra (naja naja atra), and gelonin (a plant toxin); ribosome inactivating proteins from plants, bacteria and fungi, such as restrictocin (a ribosome inactivating protein produced by *Aspergillus restrictus*), saporin (a ribosome inactivating protein from *Saponaria officinalis*), and RNase; tyrosine kinase inhibitors; ly207702 (a difluorinated purine nucleoside); liposomes containing antitumor agents (*e.g.*,

antisense oligonucleotides, plasmids which encode for toxins, methotrexate, etc.); and other antibodies or antibody fragments, such as F(ab).

[104] Those of skill in the art will readily understand and be able to make such antibody derivatives, as they are well known in the art. The antibodies may be cytotoxic on their own, or they may be used to deliver cytotoxic agents to particular locations in the body. The antibodies can be administered to individuals in need thereof as a form of passive immunization.

[105] Characterization of extracellular regions for the cell surface and secreted proteins from the protein sequence is based on the prediction of signal sequence, transmembrane domains and functional domains. Antibodies are preferably specifically immunoreactive with membrane associated proteins, particularly to extracellular domains of such proteins or to secreted proteins. Such targets are readily accessible to antibodies, which typically do not have access to the interior of cells or nuclei. However, in some applications, antibodies directed to intracellular proteins may be useful as well. Moreover, for diagnostic purposes, an intracellular protein may be an equally good target since cell lysates may be used rather than a whole cell assay.

[106] Computer programs can be used to identify extracellular domains of proteins whose sequences are known. Such programs include SMART software (Schultz et al., Proc. Natl. Acad. Sci. USA *95:* 5857-5864, 1998) and Pfam software (Bateman et al., Nucleic acids Res. *28:* 263-266, 2000) as well as PSORTII. Typically such programs identify transmembrane domains; the extracellular domains are identified as immediately adjacent to the transmembrane domains. Prediction of extracellular regions and the signal cleavage sites are only approximate. It may have a margin of error + or – 5 residues. Signal sequence can be predicted using three different methods (Nielsen et al, *Protein Engineering* 10: 1-6 ,1997, Jagla et. al, Bioinformatics 16: 245-250 , 2000, Nakai, K and Horton, P. Trends in Biochem. Sci. 24:34-35, 1999) for greater accuracy.

Similarly transmembrane (TM) domains can be identified by multiple prediction methods. (Pasquier, et. al, Protein Eng. 12:381-385, 1999, Sonnhammer et al., In Proc. of Sixth Int. Conf. on Intelligent Systems for Molecular Biology, p. 175-182 , Ed J. Glasgow, T. Littlejohn, F. Major, R. Lathrop, D. Sankoff, and C. Sensen Menlo Park, CA: AAAI Press, 1998 , Klein, et.al, Biochim. Biophys. Acta, 815:468, 1985, Nakai and Kanehisa Genomics, 14: 897-911 , 1992). In ambiguous cases, locations of functional domains in well characterized proteins are used as a guide to assign a cellular localization.

[107] Putative functions or functional domains of novel proteins can be inferred from homologous regions in the database identified by BLAST searches (Altschul et. al. Nucleic Acid Res. 25: 3389-3402, 1997) and/or from a conserved domain database such as Pfam (Bateman et.al, Nucleic Acids Res. 27:260-262 1999) BLOCKS (Henikoff, et. al, Nucl. Acids Res. 28:228-230, 2000) and SMART (Ponting, et. al, Nucleic Acid Res. 27,229-232, 1999). Extracellular domains include regions adjacent to a transmembrane domain in a single transmembrane domain protein (out-in or type I class). For multiple transmembrane domains proteins, the extracellular domain also includes those regions between two adjacent transmembrane domains (in-out and out-in). For type II transmembrane domain proteins, for which the N-terminal region is cytoplasmic, regions following the transmembrane domain is generally extracellular. Secreted proteins on the other hand do not have a transmembrane domain and hence the whole protein is considered as extracellular.

[108] Membrane associated proteins can be engineered to delete the transmembrane domains, thus leaving the extracellular portions which can bind to ligands. Such soluble forms of transmembrane receptor proteins can be used to compete with natural forms for binding to ligand. Thus such soluble forms act as inhibitors. and can be used therapeutically as anti-angiogenic agents, as diagnostic tools for the quantification of natural ligands, and in assays for the identification of small molecules which modulate or mimic the activity of a TEM:ligand complex.

[109] Alternatively, the endothelial markers themselves can be used as vaccines to raise an immune response in the vaccinated animal or human. For such uses, a protein, or immunogenic fragment of such protein, corresponding to the intracellular, extracellular or secreted TEM of interest is administered to a subject. The immogenic agent may be provided as a purified preparation or in an appropriately expressing cell. The administration may be direct, by the delivery of the immunogenic agent to the subject, or indirect, through the delivery of a nucleic acid encoding the immunogenic agent under conditions resulting in the expression of the immunogenic agent of interest in the subject. The TEM of interest may be delivered in an expressing cell, such as a purified population of tumor endothelial cells or a populations of fused tumor endothelial and dendritic cells. Nucleic acids encoding the TEM of interest may be delivered in a viral or non-viral delivery vector or vehicle. Non-human sequences encoding the human TEM of interest or other mammalian homolog can be used to induce the desired immunologic response in a human subject. For several of the TEMs of the present invention, mouse, rat or other ortholog sequences are described herein or can be obtained from the literature or using techniques well within the skill of the art.

[110] Endothelial cells can be identified using the markers which are disclosed herein as being endothelial cell specific. These include the human markers identified by SEQ ID NOS: 1-172, *i.e.*, the normal, pan-endothelial, and the tumor endothelial markers. Homologous mouse markers include tumor endothelial markers of SEQ ID NO: 182-186 and 190-194. Antibodies specific for such markers can be used to identify such cells, by contacting the antibodies with a population of cells containing some endothelial cells. The presence of cross-reactive material with the antibodies identifies particular cells as endothelial. Similarly, lysates of cells can be tested for the presence of cross-reactive material. Any known format or technique for detecting cross-reactive material can be used including, immunoblots, radioimmunoassay, ELISA, immunoprecipitation, and

immunohistochemistry. In addition, nucleic acid probes for these markers can also be used to identify endothelial cells. Any hybridization technique known in the art including Northern blotting, RT-PCR, microarray hybridization, and in situ hybridization can be used.

[111] One can identify tumor endothelial cells for diagnostic purposes, testing cells suspected of containing one or more TEMs. One can test both tissues and bodily fluids of a subject. For example, one can test a patient's blood for evidence of intracellular and membrane associated TEMs, as well as for secreted TEMs. Intracellular and/or membrane associated TEMs may be present in bodily fluids as the result of high levels of expression of these factors and/or through lysis of cells expressing the TEMs.

[112] Populations of various types of endothelial cells can also be made using the antibodies to endothelial markers of the invention. The antibodies can be used to purify cell populations according to any technique known in the art, including but not limited to fluorescence activated cell sorting. Such techniques permit the isolation of populations which are at least 50, 60, 70, 80, 90, 92, 94, 95, 96, 97, 98, and even 99 % the type of endothelial cell desired, whether normal, tumor, or pan-endothelial. Antibodies can be used to both positively select and negatively select such populations. Preferably at least 1, 5, 10, 15, 20, or 25 of the appropriate markers are expressed by the endothelial cell population.

[113] Populations of endothelial cells made as described herein, can be used for screening drugs to identify those suitable for inhibiting the growth of tumors by virtue of inhibiting the growth of the tumor vasculature.

[114] Populations of endothelial cells made as described herein, can be used for screening candidate drugs to identify those suitable for modulating angiogenesis, such as for inhibiting the growth of tumors by virtue of inhibiting the growth of endothelial cells, such as inhibiting the growth of the tumor or other undesired

vasculature, or alternatively, to promote the growth of endothelial cells and thus stimulate the growth of new or additional large vessel or microvasculature.

[115] Inhibiting the growth of endothelial cells means either regression of vasculature which is already present, or the slowing or the absence of the development of new vascularization in a treated system as compared with a control system. By stimulating the growth of endothelial cells, one can influence development of new (neovascularization) or additional vasculature development (revascularization). A variety of model screen systems are available in which to test the angiogenic and/or anti-angiogenic properties of a given candidate drug. Typical tests involve assays measuring the endothelial cell response, such as proliferation, migration, differentiation and/or intracellular interaction of a given candidate drug. By such tests, one can study the signals and effects of the test stimuli. Some common screens involve measurement of the inhibition of heparanase, endothelial tube formation on Matrigel, scratch induced motility of endothelial cells, platelet-derived growth factor driven proliferation of vascular smooth muscle cells, and the rat aortic ring assay (which provides an advantage of capillary formation rather than just one cell type).

[116] Drugs can be screened for the ability to mimic or modulate, inhibit or stimulate, growth of tumor endothelium cells and/or normal endothelial cells. Drugs can be screened for the ability to inhibit tumor endothelium growth but not normal endothelium growth or survival. Similarly, human cell populations, such as normal endothelium populations or tumor endothelial cell populations, can be contacted with test substances and the expression of tumor endothelial markers and/or normal endothelial markers determined. Test substances which decrease the expression of tumor endothelial markers (TEMs) are candidates for inhibiting angiogenesis and the growth of tumors. Conversely, markers which are only expressed in normal endothelium but not in tumor endothelium (NEMs) can be monitored. Test substances which increase the expression of such NEMs in tumor endothelium and other human cells can be identified as candidate antitumor or

anti-angiogenic drugs In cases where the activity of a TEM or NEM is known, agents can be screened for their ability to decrease or increase the activity.

[117] For those tumor endothelial markers identified as containing transmembrane regions, it is desirable to identify drug candidates capable of binding to the TEM receptors found at the cell surface. For some applications, the identification of drug candidates capable of blocking the TEM receptor from its native ligand will be desired. For some applications, the identification of a drug candidate capable of binding to the TEM receptor may be used as a means to deliver a therapeutic or diagnostic agent. For other applications, the identification of drug candidates capable of mimicing the activity of the native ligand will be desired. Thus, by manipulating the binding of a transmembrane TEM receptor:ligand complex, one may be able to promote or inhibit further development of endothelial cells and hence, vascularization.

[118] For those tumor endothelial markers identified as being secreted proteins, it is desirable to identify drug candidates capable of binding to the secreted TEM protein. For some applications, the identification of drug candidates capable of interfering with the binding of the secreted TEM it is native receptor. For other applications, the identification of drug candidates capable of mimicing the activity of the native receptor will be desired. Thus, by manipulating the binding of the secreted TEM:receptor complex, one may be able to promote or inhibit futher development of endothelial cells, and hence, vascularization.

[119] Expression can be monitored according to any convenient method. Protein or mRNA can be monitored. Any technique known in the art for monitoring specific genes' expression can be used, including but not limited to ELISAs, SAGE, microarray hybridization, Western blots. Changes in expression of a single marker may be used as a criterion for significant effect as a potential pro-angiogenic, anti-angiogenic or anti-tumor agent. However, it also may be desirable to screen for test substances which are able to modulate the expression

of at least 5, 10, 15, or 20 of the relevant markers, such as the tumor or normal endothelial markers. Inhibition of TEM protein activity can also be used as a drug screen. Human and mouse TEMS can be used for this purpose.

[120] Test substances for screening can come from any source. They can be libraries of natural products, combinatorial chemical libraries, biological products made by recombinant libraries, etc. The source of the test substances is not critical to the invention. The present invention provides means for screening compounds and compositions which may previously have been overlooked in other screening schemes. Nucleic acids and the corresponding encoded proteins of the markers of the present invention can be used therapeutically in a variety of modes. NEMs, can be used to restrict, diminish, reduce, or inhibit proliferation of tumor or other abnormal or undesirable vasculature. TEMs can be used to stimulate the growth of vasculature, such as for wound healing or to circumvent a blocked vessel. The nucleic acids and encoded proteins can be administered by any means known in the art. Such methods include, using liposomes, nanospheres, viral vectors, non-viral vectors comprising polycations, etc. Suitable viral vectors include adenovirus, retroviruses, and sindbis virus. Administration modes can be any known in the art, including parenteral, intravenous, intramuscular, intraperitoneal, topical, intranasal, intrarectal, intrabronchial, etc.

[121] Specific biological antagonists of TEMs can also be used to therapeutic benefit. For example, antibodies, T cells specific for a TEM, antisense to a TEM, and ribozymes specific for a TEM can be used to restrict, inhibit, reduce, and/or diminish tumor or other abnormal or undesirable vasculature growth. Such antagonists can be administered as is known in the art for these classes of antagonists generally. Anti-angiogenic drugs and agents can be used to inhibit tumor growth, as well as to treat diabetic retinopathy, rheumatoid arthritis, psoriasis, polycystic kidney disease (PKD), and other diseases requiring angiogenesis for their pathologies.

[122] Mouse counterparts to human TEMS can be used in mouse cancer models or in cell lines or *in vitro* to evaluate potential anti-angiogenic or anti-tumor compounds or therapies. Their expression can be monitored as an indication of effect. Mouse TEMs are disclosed in SEQ ID NO: 182-186 and 190-194. Mouse TEMs can be used as antigens for raising antibodies which can be tested in mouse tumor models. Mouse TEMs with transmembrane domains are particularly preferred for this purpose. Mouse TEMs can also be ued as vaccines to raise an immunological response in a human to the human ortholog.

[123] The above disclosure generally describes the present invention. All references disclosed herein are expressly incorporated by reference. A more complete understanding can be obtained by reference to the following specific examples which are provided herein for purposes of illustration only, and are not intended to limit the scope of the invention.

EXAMPLE 1

Visualization of vasculature of colorectal cancers

[124] The endothelium of human colorectal cancer was chosen to address the issues of tumor angiogenesis, based on the high incidence, relatively slow growth, and resistance to anti-neoplastic agents of these cancers. While certain less common tumor types, such as glioblastomas, are highly vascularized and are regarded as good targets for anti-angiogenic therapy, the importance of angiogenesis for the growth of human colorectal cancers and other common solid tumor types is less well documented.

[125] We began by staining vessels in colorectal cancers using von Willebrand Factor (vWF) as a marker. In each of 6 colorectal tumors, this examination revealed a high density of vessels throughout the tumor parenchyma (Examples in Fig. 1 A and B). Interestingly, these analyses also substantiated the importance of these

vessels for tumor growth, as endothelium was often surrounded by a perivascular cuff of viable cells, with a ring of necrotic cells evident at the periphery (Example in Fig. 1A). Although these preliminary studies suggested that colon tumors are angiogenesis-dependent, reliable markers that could distinguish vessels in colon cancers from the vessels in normal colon are currently lacking. One way to determine if such markers exist is by analyzing gene expression profiles in endothelium derived from normal and neoplastic tissue.

EXAMPLE 2

Purification of endothelial cells

[126] Global systematic analysis of gene expression in tumor and normal endothelium has been hampered by at least three experimental obstacles. First, endothelium is enmeshed in a complex tissue consisting of vessel wall components, stromal cells, and neoplastic cells, requiring highly selective means of purifying ECs for analysis. Second, techniques for defining global gene expression profiles were not available until recently. And third, only a small fraction of the cells within a tumor are endothelial, mandating the development of methods that are suitable for the analysis of global expression profiles from relatively few cells.

[127] To overcome the first obstacle, we initially attempted to purify ECs from dispersed human colorectal tissue using CD31, an endothelial marker commonly used for this purpose. This resulted in a substantial enrichment of ECs but also resulted in contamination of the preparations by hematopoietic cells, most likely due to expression of CD31 by macrophages. We therefore developed a new method for purifying ECs from human tissues using P1H12, a recently described marker for ECs. Unlike CD31, P1H12 was specifically expressed on the ECs of both colorectal tumors and normal colorectal mucosa. Moreover, immunofluorescence staining of normal and cancerous colon with a panel of known cell surface endothelial markers (e.g. VE-cadherin, CD31 and CD34)

revealed that P1H12 was unique in that it stained all vessels including microvessels (see Fig. 2A and data not shown). In addition to selection with P1H12, it was necessary to optimize the detachment of ECs from their neighbors without destroying their cell surface proteins as well as to employ positive and negative affinity purifications using a cocktail of antibodies (Fig. 2B). The ECs purified from normal colorectal mucosa and colorectal cancers were essentially free of epithelial and hematopoietic cells as judged by RT-PCR (Fig. 2C) and subsequent gene expression analysis (see below).

EXAMPLE 3

Comparison of tumor and normal endothelial cell expression patterns

[128] To overcome the remaining obstacles, a modification of the Serial Analysis of Gene Expression (SAGE) technique was used. SAGE associates individual mRNA transcripts with 14 base pair tags derived from a specific position near their 3' termini. The abundance of each tag provides a quantitative measure of the transcript level present within the mRNA population studied. SAGE is not dependent on pre-existing databases of expressed genes, and therefore provides an unbiased view of gene expression profiles. This feature is particularly important in the analysis of cells that constitute only a small fraction of the tissue under study, as transcripts from these cells are unlikely to be well represented in extant EST databases. We adapted the SAGE protocol so that it could be used on small numbers of purified ECs obtained from the procedure outlined in Fig. 2B. A library of ~100,000 tags from the purified ECs of a colorectal cancer, and a similar library from the ECs of normal colonic mucosa from the same patient were generated. These ~193,000 tags corresponded to over 32,500 unique transcripts. Examination of the expression pattern of hematopoietic, epithelial and endothelial markers confirmed the purity of the preparations (Fig. 2D).

EXAMPLE 4

Markers of normal and tumor endothelium

[129] We next sought to identify Pan Endothelial Markers (PEMs), that is, transcripts that were expressed at significantly higher levels in both normal and tumor associated endothelium compared to other tissues. To identify such PEMs, tags expressed at similar levels in both tumor and normal ECs were compared to ~ 1.8 million tags from a variety of cell lines derived from tumors of non-endothelial origin. This simple comparison identified 93 transcripts that were strikingly EC-specific, i.e. expressed at levels at least 20-fold higher in ECs in vivo compared to non-endothelial cells in culture. The 15 tags corresponding to characterized genes which were most highly and specifically expressed in endothelium are shown in Table 1A. Twelve of these 15 most abundant endothelial transcripts had been previously shown to be preferentially expressed in endothelium , while the other 3 genes had not been associated with endothelium in the past (Table 1A). These data sets also revealed many novel PEMs, which became increasingly prevalent as tag expression levels decreased (Table 1B). For many of the transcripts, their endothelial origin was confirmed by SAGE analysis of ~401,000 transcripts derived from primary cultures of human umbilical vein endothelial cells (HUVEC) and human dermal microvascular endothelial cells (HMVEC) (Table 1 A and B). To further validate the expression of these PEMs in vivo, we developed a highly sensitive non-radioactive in situ hybridization method that allowed the detection of transcripts expressed at relatively low levels in frozen sections of human tissues. Two uncharacterized markers, PEM3 and PEM6, were chosen for this analysis. In each case, highly specific expression was clearly limited to vascular ECs in both normal and neoplastic tissues (Fig. 3 A and B and data not shown). These data also suggest that ECs maintained in culture do not completely recapitulate expression patterns observed in vivo. For example, Hevin and several other PEM's were expressed at high levels in both tumor and normal

ECs in vivo, but few or no transcripts were detected in cultured HUVEC or HMVEC (Table 1). The source of the Hevin transcripts was confirmed to be endothelium by in situ hybridization in normal and malignant colorectal tissue (Fig. 3C).

[130] Many of the markers reported in Table 1 were expressed at significantly higher levels than previously characterized genes commonly associated with ECs. For example, the top 25 markers were all expressed at greater than 200 copies per cell. In contrast, the receptors for VEGF (VEGFR-1 and VEGFR-2) were expressed at less than 20 copies per cell. Interestingly, VEGFR2 (KDR), which had previously been reported to be up-regulated in vessels during colon cancer progression , was found to be expressed in both normal and neoplastic colorectal tissue (Fig. 3 D and E). The lack of specificity of this gene was in accord with the SAGE data, which indicated that the VEGFR was expressed at 12 copies per cell in both normal and tumor endothelium.

EXAMPLE 5

Tumor *versus* normal endothelium

[131] We next attempted to identify transcripts that were differentially expressed in endothelium derived from normal or neoplastic tissues. This comparison revealed 33 tags that were preferentially expressed in normal-derived endothelium at levels at least 10-fold higher than in tumor-derived endothelium. Conversely, 46 tags were expressed at 10-fold or higher levels in tumor vessels. Because those transcripts expressed at higher levels in tumor endothelium are most likely to be useful in the future for diagnostic and therapeutic purposes, our subsequent studies focussed on this class. Of the top 25 tags most differentially expressed, 12 tags corresponded to 11 previously identified genes, one with an alternative polyadenylation site (see Table 2). Of these 10 genes, 6 have been recognized as markers associated with angiogenic vessels. The remaining 14 tags corresponded

to uncharacterised genes, most of which have only been deposited as ESTs (Table 2).

[132] To validate the expression patterns of these genes, we chose to focus on 9 Tumor Endothelial Markers (BSC-TEM 1-9; TEM 1, 2, 5, 9, 16, 17, 19, and 22) for which EST sequences but no other information was available (Table 2). These tags were chosen simply because they were among the most differentially expressed on the list and because we were able to obtain suitable probes. In many cases, this required obtaining near full-length sequences through multiple rounds of sequencing and cDNA walking (See accession numbers in Table 2). RT-PCR analysis was then used to evaluate the expression of the corresponding transcripts in purified ECs derived from normal and tumor tissues of two patients different from the one used to construct the SAGE libraries. As shown in Fig. 4 A, the vWF gene, expected to be expressed in both normal and tumor endothelium on the basis of the SAGE data as well as previous studies, was expressed at similar levels in normal and tumor ECs from both patients, but was not expressed in purified tumor epithelial cells. As expected, PEM2 displayed a pattern similar to vWF. In contrast, all 9 TEMs chosen for this analysis were prominently expressed in tumor ECs, but were absent or barely detectable in normal ECs (Table 3 and examples in Fig. 4A). It is important to note that these RT-PCR assays were extremely sensitive indicators of expression, and the absence of detectable transcripts in the normal endothelium, combined with their presence in tumor endothelial RNAs even when diluted 100-fold, provides compelling confirmatory evidence for their differential expression. These results also show that these transcripts were not simply expressed differentially in the ECs of the original patient, but were characteristic of colorectal cancer endothelium in general.

[133] It could be argued that the results noted above were compromised by the possibility that a small number of non-endothelial cells contaminated the cell populations used for SAGE and RT-PCR analyses, and that these non-endothelial

cells were responsible for the striking differences in expression of the noted transcripts. To exclude this possibility, we performed in situ hybridization on normal and neoplastic colon tissue. In every case where transcripts could be detected (BSC-TEM 1, 3, 4, 5, 7, 8, and 9; TEM 1, 5, 9, 17, and 19), they were specifically localized to ECs (Table 3 and examples in Fig. 4 B and C). Although caution must be used when interpreting negative in situ hybridization results, none of the TEMs were expressed in vascular ECs associated with normal colorectal tissue even though vWF and Hevin were clearly expressed (Table 3).

EXAMPLE 6

Tumor endothelium markers are expressed in multiple tumor types

[134] Were these transcripts specifically expressed in the endothelium within primary colorectal cancers, or were they characteristic of tumor endothelium in general? To address this question, we studied the expression of a representative TEM (BSC-TEM7; TEM 17) in a liver metastasis from a colorectal cancer, a sarcoma, and in primary cancers of the lung, pancreas, breast and brain. As shown in Fig. 4, the transcript was found to be expressed specifically in the endothelium of each of these cancers, whether metastatic (Fig. 4D) or primary (Fig. 4E-I). Analysis of the other six TEMs, (BSC-TEM 1, 3,4,5, 7, 8 and 9; TEM 1, 5, 9, 17, and 19) revealed a similar pattern in lung tumors, brain tumors, and metastatic lesions of the liver (see Table 3).

EXAMPLE 7

Tumor endothelium markers are neo-angiogenic

[135] Finally, we asked whether these transcripts were expressed in angiogenic states other than that associated with tumorigenesis. We thus performed in situ hybridizations on corpus luteum tissue as well as healing wounds. Although there

were exceptions, we found that these transcripts were generally expressed both in the corpus luteum and in the granulation tissue of healing wounds (Table 3 and example in Fig. 4J). In all tissues studied, expression of the genes was either absent or exclusively confined to the EC compartment.

References and Notes

The disclosure of each reference cited is expressly incorporated herein.

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8. The original EC isolation protocol was the same as that shown in Fig. 2B except that dispersed cells were stained with anti-CD31 antibodies instead of anti-P1H12, and magnetic beads against CD64 and CD14 were not included in the negative selection. After generating 120,000 SAGE tags from these two EC preparations, careful analysis of the SAGE data revealed that, in addition to endothelial-specific markers, several macrophage-specific markers were also present.

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11. In order to reduce the minimum amount of starting material required from ~50 million cells to ~50,000 cells (i.e. ~1000-fold less) we and others (38) have introduced

several modifications to the original SAGE protocol. A detailed version of our modified "MicroSAGE" protocol is available from the authors upon request.

12. 96,694 and 96,588 SAGE tags were analyzed from normal and tumor derived ECs, respectively, and represented 50,298 unique tags. A conservative estimate of 32,703 unique transcripts was derived by considering only those tags observed more than once in the current data set or in the 134,000 transcripts previously identified in human transcriptomes (39).

13. To identify endothelial specific transcripts, we normalized the number of tags analyzed in each group to 100,000, and limited our analysis to transcripts that were expressed at levels at least 20-fold higher in ECs than in non-endothelial cell lines in culture and present at fewer than 5 copies per 100,000 transcripts in non-endothelial cell lines and the hematopoietic fraction (~57,000 tags)(41). Non-endothelial cell lines consisted of 1.8x106 tags derived from a total of 14 different cancer cell lines including colon, breast, lung, and pancreatic cancers, as well as one non-transformed keratinocyte cell line, two kidney epithelial cell lines, and normal monocytes. A complete list of PEMs is available at www.sagenet.org\angio\table1.htm.

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26. For non-radioactive in situ hybridization, digoxigenin (DIG)-labelled sense and anti-sense riboprobes were generated through PCR by amplifying 500-600 bp products and incorporating a T7 promoter into the anti-sense primer. In vitro transcription was performed using DIG RNA labelling reagents and T7 RNA polymerase (Roche, Indianapolis, IN). Frozen tissue sections were fixed with 4 % paraformaldehyde, permeabilized with pepsin, and incubated with 200 ng/ml of riboprobe overnight at 55oC. For signal amplification, a horseradish peroxidase (HRP) rabbit anti-DIG antibody (DAKO, Carpinteria, CA) was used to catalyse the deposition of Biotin-Tyramide (from GenPoint kit, DAKO). Further amplification was achieved by adding HRP rabbit anti-biotin (DAKO), biotin-tyramide, and then alkaline-phosphatase (AP) rabbit anti-biotin (DAKO). Signal was detected using the AP substrate Fast Red TR/Napthol AS-MX (Sigma, St. Louis, MO), and cells were counterstained with hematoxylin unless otherwise indicated. A detailed protocol including the list of primers used to generate the probes can be obtained from the authors upon request.

27. Transcript copies per cell were calculated assuming an average cell contains 300,000 transcripts.

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31. Endothelial-specific transcripts were defined as those expressed at levels at least 5-fold higher in ECs in vivo than in non-endothelial cell lines in culture (13), and present at no more than 5 copies per 100,000 transcripts in non-endothelial cell lines and the hematopoietic cell fraction (41). Transcripts showing statistically different levels of expression ($P < 0.05$) were then identified using Monte Carlo analysis as previously described (40). Transcripts preferentially expressed in normal endothelium were then defined as those expressed at levels at least 10-fold higher in normal endothelium than in tumor endothelium. Conversely, tumor endothelial transcripts were at least 10-fold higher in tumor versus normal endothelium. See www.sagenet.org\angio\table2.htm and www.sagenet.org\angio\table3.htm for a complete list of differentially expressed genes.

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41. Human colon tissues were obtained within ½ hour after surgical removal from patients. Sheets of epithelial cells were peeled away from normal tissues with a glass slide following treatment with 5 mM DDT, then 10 mM EDTA, leaving the lamina propria intact. After a 2h incubation in collagenase at 37 oC, cells were filtered sequentially through 400 um, 100 um, 50 um and 25 um mesh, and spun through a 30 % pre-formed Percoll gradient to pellet RBCs. Epithelial cells (Epithelial Fraction), which were found to non-specifically bind magnetic beads, were removed using Dynabeads coupled to BerEP4 (Dynal, Lake Success, NY). Subsequently, macrophages and other leukocytes (Hematopoietic Fraction) were removed using a cocktail of beads coupled to anti-CD45, anti-CD14 and anti-CD64 (Dynal). The remaining cells were stained with P1H12 antibody, purified with anti-mouse IgG-coupled magnetic beads, and lysed in mRNA lysis buffer. A detailed protocol can be obtained from the authors upon request.

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Sequence name	SEQ ID NO:
PEM 1	1
PEM 2	2
PEM 3	3
PEM 4	4
PEM 5	5
PEM 6	6
PEM 7	7
PEM 8	8
PEM 9	9
PEM 10	10
PEM 11	11
PEM 12	12
PEM 13	13
PEM 14	14
PEM 15	15
PEM 16	16
PEM 17	17
PEM 18	18
PEM 19	19
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PEM 26	26
PEM 27	27
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PEM 31	31
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PEM 33	33
PEM 34	34
PEM 35	35

SEQ ID NO:	Sequence name
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NEM 33	172
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TEM 2 DNA	174
TEM 7 DNA	175
TEM 8 DNA	176
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TEM 2 Protein	178
TEM 8 Protein	179
TEM 5 DNA	180
TEM 7B DNA	181
mTEM 1 DNA	182
mTEM 5 DNA	183
mTEM 7 DNA	184
mTEM 7B DNA	185
mTEM 8 DNA	186
TEM 8 Protein	187
TEM 5 Protein	188
TEM 7B Protein	189
mTEM 1 Protein	190
mTEM 5 Protein	191

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175	TEM 7 DNA
176	TEM 8 DNA
177	TEM 1 Protein
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179	TEM 8 Protein
180	TEM 5 DNA
181	TEM 7B DNA
182	mTEM 1 DNA
183	mTEM 5 DNA
184	mTEM 7 DNA
185	mTEM 7B DNA
186	mTEM 8 DNA
187	TEM 8 Protein
188	TEM 5 Protein
189	TEM 7B Protein
190	mTEM 1 Protein
191	mTEM 5 Protein

mTEM 7 Protein	192
mTEM 7b Protein	193
mTEM 8 Protein	194
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TEM 1 Protein	196
TEM 2 DNA	197
TEM 2 Protein	198
TEM 3 DNA	199
TEM 3 Protein	200
TEM 4 DNA	201
TEM 4 Protein	202
TEM 5 DNA	203
TEM 5 Protein	204
TEM 6 DNA	205
TEM 6 Protein	206
TEM 7 DNA	207
TEM 7 Protein	208
TEM 8 DNA	209
TEM 8 Protein	210
TEM 9 DNA	211
TEM 9 Protein	212
TEM 10 DNA	213
TEM 10 Protein	214
TEM 11 DNA	215
TEM 11 Protein	216
TEM 12 DNA	217
TEM 12 Protein	218
TEM 13 DNA	219
TEM 13 Protein	220
TEM 14a DNA	221
TEM 14b DNA	222
TEM 14a Protein	223
TEM 14b Protein	224
TEM 15 DNA	225
TEM 15 Protein	226
TEM 16 DNA	227
TEM 16 Protein	228
TEM 17 DNA	229
TEM 17 Protein	230

192	mTEM 7 Protein
193	mTEM 7b Protein
194	mTEM 8 Protein
195	TEM 1 DNA
196	TEM 1 Protein
197	TEM 2 DNA
198	TEM 2 Protein
199	TEM 3 DNA
200	TEM 3 Protein
201	TEM 4 DNA
202	TEM 4 Protein
203	TEM 5 DNA
204	TEM 5 Protein
205	TEM 6 DNA
206	TEM 6 Protein
207	TEM 7 DNA
208	TEM 7 Protein
209	TEM 8 DNA
210	TEM 8 Protein
211	TEM 9 DNA
212	TEM 9 Protein
213	TEM 10 DNA
214	TEM 10 Protein
215	TEM 11 DNA
216	TEM 11 Protein
217	TEM 12 DNA
218	TEM 12 Protein
219	TEM 13 DNA
220	TEM 13 Protein
221	TEM 14a DNA
222	TEM 14b DNA
223	TEM 14a Protein
224	TEM 14b Protein
225	TEM 15 DNA
226	TEM 15 Protein
227	TEM 16 DNA
228	TEM 16 Protein
229	TEM 17 DNA
230	TEM 17 Protein

TEM 19 DNA	231
TEM 19 Protein	232
TEM 20 DNA	233
TEM 20 Protein	234
TEM 21 DNA	235
TEM 21 Protein	236
TEM 22 DNA	237
TEM 22 Protein	238
TEM 24 DNA	239
TEM 24 Protein	240
TEM 25 DNA	241
TEM 25 Protein	242
TEM 27 DNA	243
TEM 27 Protein	244
TEM 28 DNA	245
TEM 28 Protein	246
TEM 29 DNA	247
TEM 29 Protein	248
TEM 30 DNA	249
TEM 30 Protein	250
TEM 31 DNA	251
TEM 31 Protein	252
TEM 33 DNA	253
TEM 33 Protein	254
TEM 35 DNA	255
TEM 35 Protein	358
TEM 36 DNA	256
TEM 36 Protein	257
TEM 37 DNA	258
TEM 37 Protein	259
TEM 38 DNA	260
TEM 38 Protein	261
TEM 39 DNA	262
TEM 39 Protein	263
TEM 40 DNA	264
TEM 40 Protein	265
TEM 41 DNA	266
TEM 41 Protein	267
TEM 42 DNA	268

231	TEM 19 DNA
232	TEM 19 Protein
233	TEM 20 DNA
234	TEM 20 Protein
235	TEM 21 DNA
236	TEM 21 Protein
237	TEM 22 DNA
238	TEM 22 Protein
239	TEM 24 DNA
240	TEM 24 Protein
241	TEM 25 DNA
242	TEM 25 Protein
243	TEM 27 DNA
244	TEM 27 Protein
245	TEM 28 DNA
246	TEM 28 Protein
247	TEM 29 DNA
248	TEM 29 Protein
249	TEM 30 DNA
250	TEM 30 Protein
251	TEM 31 DNA
252	TEM 31 Protein
253	TEM 33 DNA
254	TEM 33 Protein
255	TEM 35 DNA
256	TEM 36 DNA
257	TEM 36 Protein
258	TEM 37 DNA
259	TEM 37 Protein
260	TEM 38 DNA
261	TEM 38 Protein
262	TEM 39 DNA
263	TEM 39 Protein
264	TEM 40 DNA
265	TEM 40 Protein
266	TEM 41 DNA
267	TEM 41 Protein
268	TEM 42 DNA
269	TEM 42 Protein

TEM 42 Protein	269
TEM 44 DNA	270
TEM 44 Protein	271
TEM 45 DNA	272
TEM 45 Protein	273
TEM 46 DNA	274
TEM 46 Protein	275
NEM 4 DNA	276
NEM 4 Protein	277
NEM 14 DNA	278
NEM 14 Protein	279
NEM 17 DNA	280
NEM 17 Protein	281
NEM 22 DNA	282
NEM 22 Protein	283
NEM 23 DNA	284
NEM 23 Protein	285
NEM 23 Secreted	286
NEM 23 Short	287
NEM 33 DNA	288
NEM 33 Protein	289
mTEM 1 DNA	290
mTEM 1 Protein	291
mTEM 2 DNA	292
mTEM 2 Protein	293
mTEM 3 DNA	298
mTEM 3 Protein	299
mTEM 9 DNA	294
mTEM 9 Protein	295
mTEM 13 DNA	302
mTEM 13 Protein	303
mTEM 17 DNA	296
mTEM 17 Protein	297
mTEM 19 DNA	300
mTEM 19 Protein	301
mTEM 22 DNA	304
mTEM 22 Protein	305
mTEM 30 DNA	306
mTEM 30 Protein	307

270	TEM 44 DNA
271	TEM 44 Protein
272	TEM 45 DNA
273	TEM 45 Protein
274	TEM 46 DNA
275	TEM 46 Protein
276	NEM 4 DNA
277	NEM 4 Protein
278	NEM 14 DNA
279	NEM 14 Protein
280	NEM 17 DNA
281	NEM 17 Protein
282	NEM 22 DNA
283	NEM 22 Protein
284	NEM 23 DNA
285	NEM 23 Protein
286	NEM 23 Secreted
287	NEM 23 Short
288	NEM 33 DNA
289	NEM 33 Protein
290	mTEM 1 DNA
291	mTEM 1 Protein
292	mTEM 2 DNA
293	mTEM 2 Protein
294	mTEM 9 DNA
295	mTEM 9 Protein
296	mTEM 17 DNA
297	mTEM 17 Protein
298	mTEM 3 DNA
299	mTEM 3 Protein
300	mTEM 19 DNA
301	mTEM 19 Protein
302	mTEM 13 DNA
303	mTEM 13 Protein
304	mTEM 22 DNA
305	mTEM 22 Protein
306	mTEM 30 DNA
307	mTEM 30 Protein
308	TEM 2 tag

TEM 2 tag	308
TEM 1 long tag	309
TEM 3 long tag	310
TEM 4 long tag	311
TEM 5 long tag	312
TEM 5 long tag	313
TEM 6 long tag	314
TEM 7 long tag	315
TEM 8 long tag	316
TEM 9 long tag	317
TEM 10 long tag	318
TEM 10 long tag	319
TEM 10 long tag	320
TEM 11 long tag	321
TEM 12 long tag	322
TEM 13 long tag	323
TEM 13 long tag	324
TEM 14 long tag	325
TEM 15 long tag	326
TEM 15 long tag	327
TEM 16 long tag	328
TEM 17 long tag	329
TEM 19 long tag	330
TEM 21 long tag	331
TEM 21 long tag	332
TEM 22 long tag	333
TEM 22 long tag	334
TEM 23 long tag	335
TEM 24 long tag	336
TEM 25 long tag	337
TEM 25 long tag	338
TEM 28 long tag	339
TEM 30 long tag	340
TEM 31 long tag	341
TEM 32 long tag	342
TEM 33 long tag	343
TEM 33 long tag	344
TEM 35 long tag	345
TEM 36 long tag	346

309	TEM 1 long tag
310	TEM 3 long tag
311	TEM 4 long tag
312	TEM 5 long tag
313	TEM 5 long tag
314	TEM 6 long tag
315	TEM 7 long tag
316	TEM 8 long tag
317	TEM 9 long tag
318	TEM 10 long tag
319	TEM 10 long tag
320	TEM 10 long tag
321	TEM 11 long tag
322	TEM 12 long tag
323	TEM 13 long tag
324	TEM 13 long tag
325	TEM 14 long tag
326	TEM 15 long tag
327	TEM 15 long tag
328	TEM 16 long tag
329	TEM 17 long tag
330	TEM 19 long tag
331	TEM 21 long tag
332	TEM 21 long tag
333	TEM 22 long tag
334	TEM 22 long tag
335	TEM 23 long tag
336	TEM 24 long tag
337	TEM 25 long tag
338	TEM 25 long tag
339	TEM 28 long tag
340	TEM 30 long tag
341	TEM 31 long tag
342	TEM 32 long tag
343	TEM 33 long tag
344	TEM 33 long tag
345	TEM 35 long tag
346	TEM 36 long tag
347	TEM 37 long tag

TEM 37 long tag	347
TEM 38 long tag	348
TEM 38 long tag	349
TEM 39 long tag	350
TEM 40 long tag	351
TEM 41 long tag	352
TEM 42 long tag	353
TEM 43 long tag	354
TEM 44 long tag	355
TEM 45 long tag	356
TEM 46 long tag	357

348	TEM 38 long tag
349	TEM 38 long tag
350	TEM 39 long tag
351	TEM 40 long tag
352	TEM 41 long tag
353	TEM 42 long tag
354	TEM 43 long tag
355	TEM 44 long tag
356	TEM 45 long tag
357	TEM 46 long tag
358	TEM 35 Protein

CLAIMS

1. An isolated molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 9, 17, 19, and 44, as shown in SEQ ID NO: 196, 212, 230, 232, and 271, respectively.
2. The isolated molecule of claim 1 which is an in tact antibody molecule.
3. The isolated molecule of claim 1 which is a single chain variable region (ScFv).
4. The isolated molecule of claim 1 which is a monoclonal antibody.
5. The isolated molecule of claim 1 which is a humanized antibody.
6. The isolated molecule of claim 1 which is a human antibody.
7. The isolated molecule of claim 1 which is bound to a cytotoxic moiety.
8. The isolated molecule of claim 1 which is bound to a therapeutic moiety.
9. The isolated molecule of claim 1 which is bound to a detectable moiety.
10. The isolated molecule of claim 1 which is bound to an anti-tumor agent.

11. A method of inhibiting neoangiogenesis, comprising:

administering to a subject in need thereof an effective amount of an isolated molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 9, 17, 19, 22, and 44, as shown in SEQ ID NO: 196, 212, 230, 232, 238, and 271, respectively, whereby neoangiogenesis is inhibited.

12. The method of claim 11 wherein the subject bears a vascularized tumor.
13. The method of claim 11 wherein the subject has polycystic kidney disease.
14. The method of claim 11 wherein the subject has diabetic retinopathy.
15. The method of claim 11 wherein the subject has rheumatoid arthritis.
16. The method of claim 11 wherein the subject has psoriasis.

17. A method of inhibiting tumor growth, comprising:

administering to a human subject bearing a tumor an effective amount of an isolated molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 9, 17, 19, 22, and 44, as shown in SEQ ID NO: 196, 212, 230, 232, 238, and 271, respectively, whereby growth of the tumor is inhibited.

18. An isolated molecule comprising an antibody variable region which specifically binds to a TEM protein selected from the group consisting of: 9, 17, 19, and 44, as shown in SEQ ID NO: 212, 230, 232, and 271, respectively.
19. The isolated molecule of claim 18 which is a single chain variable region (ScFv).
20. The isolated molecule of claim 18 which is a monoclonal antibody.
21. The isolated molecule of claim 18 which is a humanized antibody.
22. The isolated molecule of claim 18 which is a human antibody.
23. The isolated molecule of claim 18 which is bound to a cytotoxic moiety.
24. The isolated molecule of claim 18 which is bound to a therapeutic moiety.
25. The isolated molecule of claim 18 which is bound to a detectable

moiety.

26. The isolated molecule of claim 18 which is bound to an anti-tumor agent.
27. The isolated molecule of claim 18 which is an in tact antibody molecule.
28. An isolated and purified human transmembrane protein selected from the group consisting of: TEM 9, 17, and 19 as shown in SEQ ID NO: 212, 230, and 232, respectively.
29. An isolated and purified nucleic acid molecule comprising a coding sequence for a transmembrane TEM selected from the group consisting of: : TEM 9, 17, and 19 as shown in SEQ ID NO: 212, 230, 232, respectively.
30. The isolated and purified nucleic acid molecule of claim 29 which comprises a coding sequence selected from those shown in SEQ ID NO: 211, 229, and 231,.
31. A recombinant host cell which comprises a nucleic acid molecule comprising a coding sequence for a transmembrane TEM selected from the group consisting of: TEM 9, 17, and 19 as shown in SEQ ID NO: 212, 230, and 232, respectively.
32. The recombinant host cell of claim 31 which comprises a coding sequence selected from those shown in SEQ ID NO: 211, 229, and 231.
33. A method of inducing an immune response in a mammal, comprising:

administering to the mammal a nucleic acid molecule comprising a coding sequence for a human transmembrane protein selected from the group consisting of: TEM 1, 9, 13, 17, 19, 22, 30, and 44 as shown in SEQ ID NO: 196, 212, 220, 230, 232, 238, 250 and 271, respectively, whereby an immune response to the human transmembrane protein is induced in the mammal.

34. The method of claim 33 wherein the coding sequence is shown in SEQ ID NO: 195, 211, 219, 229, 231, 237, 249, 270.

35. A method of inducing an immune response in a mammal, comprising:

administering to the mammal a purified human transmembrane protein selected from the group consisting of: TEM 1, 9, 13, 17, 19, 22, 30, and 44 as shown in SEQ ID NO: 196, 212, 220, 230, 232, 238, 250 and 271 , respectively, whereby an immune response to the human transmembrane protein is induced in the mammal.

36. A method for identification of a ligand involved in endothelial cell regulation, comprising:

contacting a test compound with an isolated and purified human trasmembrane protein selected from the group consisting of 1, 9, 13, 17, 19, 30, and 44 as shown in SEQ ID NO: 196, 212, 220, 230, 250, 232 and 271;

contacting the isolated and purified human trasmembrane protein with a molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 9, 13, 17, 19, 30, and 44 as shown in SEQ ID NO: 196, 212, 220, 230, 250, 232 and 271, respectively;

determining binding of the molecule comprising an antibody variable region to the human transmembrane protein, wherein a test compound which diminishes the binding of the molecule comprising an antibody variable region to the human transmembrane protein is identified as a ligand involved in endothelial cell regulation.

37. A method for identification of a ligand involved in endothelial cell regulation, comprising:

contacting a test compound with a cell comprising a human transmembrane protein selected from the group consisting of 1, 9, 17, and 19 as shown in SEQ ID NO: 196, 212, 230, and 232;

contacting the cell with a molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 9, 17, and 19 as shown in SEQ ID NO: 196, 212, 230, and 232, respectively;

determining binding of the molecule comprising an antibody variable region to the cell, wherein a test compound which diminishes the binding of the molecule comprising an antibody variable region to the cell is identified as a ligand involved in endothelial cell regulation.

38. A soluble form of a human transmembrane protein selected from the group consisting of: TEM 1, 9, 17, 19, 22, 30 and 44 as shown in SEQ ID NO: 196, 212, 230, 232, 238, 250, and 271, respectively, wherein the soluble forms lack transmembrane domains.

39. The soluble form of claim 38 wherein the soluble form consists of an extracellular domain of the human transmembrane protein.

40. A method of inhibiting neoangiogenesis in a patient, comprising: administering to the patient a soluble form of a human transmembrane protein according to claim 38, whereby neoangiogenesis in the patient is inhibited.

41. A method of inhibiting neoangiogenesis in a patient, comprising: administering to the patient a soluble form of a human transmembrane protein according to claim 39, whereby neoangiogenesis in the patient is inhibited.

42. The method of claim 40 wherein the patient bears a vascularized tumor.

43. The method of claim 41 wherein the patient bears a vascularized tumor.

44. The method of claim 40 wherein the patient has polycystic kidney disease.

45. The method of claim 40 wherein the patient has diabetic retinopathy.

46. The method of claim 40 wherein the patient has rheumatoid arthritis.

47. The method of claim 40 wherein the patient has psoriasis.

48. The method of claim 41 wherein the patient has polycystic kidney disease.

49. The method of claim 41 wherein the patient has diabetic retinopathy.

50. The method of claim 41 wherein the patient has rheumatoid arthritis.

51. The method of claim 41 wherein the patient has psoriasis.

52. A method of identifying regions of neoangiogenesis in a patient, comprising:

administering to a patient a molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 9, 13, 17, 19, 22, 30, and 44, as shown in SEQ ID NO: 196, 212, 220, 230, 232, 238, 250, and 271, respectively, wherein the molecule is bound to a detectable moiety; and

detecting the detectable moiety in the pateint, thereby identifying neoangiogenesis.

53. A method of screening for neoangiogenesis in a patient, comprising:

contacting a body fluid collected from the patient with a molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 9, 17, 19, and 44, as shown in SEQ ID NO: 196, 212, 230, 232, and 271, respectively, wherein detection of cross-reactive material in the body fluid with the molecule indicates neoangiogenesis in the patient.

54. A method of screening for neoangiogenesis in a patient, comprising:

contacting a body fluid collected from the patient with a molecule comprising an antibody variable region which specifically binds to a TEM protein selected from the group consisting of: 4, 6, 7, 10, 12, 14, 25, 27, 31, 36, 37, 38, 39, as shown in SEQ ID NO: 202, 206, 208, 214, 218, 223 & 224, 242, 244, 252, 257, 259, 261, and 263, respectively, wherein detection of cross-reactive material in the body fluid with the molecule indicates neoangiogenesis in the patient.

55. A method of promoting neoangiogenesis in a patient, comprising:

administering to a patient in need of neoangiogenesis a TEM protein selected from the group consising of: 4, 6, 7, 10, 12, 14, 20, 25, 27, 31, 36, 37, 38, 39, and 40, as shown in SEQ ID NO: 202, 206, 208, 214, 218, 223 & 224, 234, 242, 244, 252, 257, 259, 261. 263, and 265, whereby neoangiogenesis in the patient is stimulated.

56. A method of promoting neoangiogenesis in a patient, comprising:

administering to a patient in need of neoangiogenesis a nucleic acid molecule encoding a TEM protein selected from the group consising of: 4, 6, 7, 10, 12, 14, 20, 25, 27, 31, 36, 37, 38, 39, and 40, as shown in SEQ ID NO: 202, 206, 208, 214, 218, 223 & 224, 234, 242, 244, 252, 257, 259, 261. 263, and 265, whereby the TEM protein is expressed and neoangiogenesis in the patient is stimulated.

57. A method of screening for neoangiogenesis in a patient, comprising:

detecting a TEM protein selected from the group consisting of: 4, 6, 7, 10, 12, 14, 20, 25, 27, 31, 36, 37, 38, 39, and 40, as shown in SEQ ID NO: 202, 206, 208, 214, 218, 223 & 224, 234, 242, 244, 252, 257, 259, 261. 263, and 265, respectively, in a body fluid collected from the patient, wherein detection of the TEM protein indicates neoangiogenesis in the patient.

58. A method of screening for neoangiogenesis in a patient, comprising:

detecting in a body fluid collected from the patient a nucleic acid encoding a TEM protein selected from the group consisting of: 4, 6, 7, 10, 12, 14, 20, 25, 27, 31, 36, 37, 38, 39, and 40, wherein the nucleic acid is selected from the group consisting of those shown in SEQ ID NO: 201, 205, 207, 213, 217, 221 & 222, 233, 241, 243, 251, 256, 258, 260, 262, and 264, respectively, wherein detection of the TEM protein indicates neoangiogenesis in the patient.

59. An isolated and purified nucleic acid molecule which encodes a NEM protein selected from the group consisting of: 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289.

60. The nucleic acid molecule of claim 60 wherein the nucleic acid molecule comprises a coding sequence as shown in SEQ ID NO: 278, 282, 284, and 288 .

61. A recombinant host cell which comprises a nucleic acid according to claim 60.

62. An isolated and purified NEM protein selected from the group consising of: 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289, respectively.

63. An isolated molecule comprising an antibody variable region which specifically binds to a NEM protein selected from the group

consisting of: 14, 22, 23, and 33, as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289.

64. A method of inhibiting neoangiogenesis, comprising:

administering to a subject in need thereof an effective amount of a NEM protein selected from the group consising of: 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289, whereby neoangiogenesis is inhibited.

65. A method to identify candidate drugs for treating tumors, comprising:

contacting cells which express one or more TEM genes selected from the group consisting of: 1, 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 30, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: 195, 197, 201, 203, 205, 207, 209, 211, 213, 215, 217, 219, 221 & 222, 225, 227, 229, 231, 233, 235, 237, 239, 241, 243, 245, 247, 249, 251, 253, 255, 256, 258, 260, 262, 266, 268, 270, 272, and 274, respectively, with a test compound;

determining expression of said one or more TEM genes by hybridization of mRNA of said cells to a nucleic acid probe which is complementary to said mRNA; and

identifying a test compound as a candidate drug for treating tumors if it decreases expression of said one or more TEM genes.

66. The method of claim 66 wherein the cells are endothelial cells.

67. The method of claim 66 wherein the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more TEMs.

68. A method to identify candidate drugs for treating tumors, comprising:

contacting cells which express one or more TEM proteins selected from the group consisting of: 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 30, 31, 33, 35, 36, 37, 38, 39, 41,

42, 44, 45, and 46 as shown in SEQ ID NO: 198, 202, 204, 206, 208, 210, 212, 214, 216, 218, 223 & 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 358, 257, 259, 261, 263, 267, 269, 271, 273, and 275, respectively, with a test compound;

determining amount of said one or more TEM proteins in said cells; and

identifying a test compound as a candidate drug for treating tumors if it decreases the amount of one more TEM proteins in said cells.

69. The method of claim 69 wherein the cells are endothelial cells.

70. The method of claim 69 wherein the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more TEMs.

71. A method to identify candidate drugs for treating tumors, comprising:

contacting cells which express one or more TEM proteins selected from the group consisting of: 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 40, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: 198, 202, 204, 206, 208, 210, 212, 214, 216, 218, 223 & 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 358, 257, 259, 261, 263, 267, 269, 271, 273, and 275 respectively, with a test compound;

determining activity of said one or more TEM proteins in said cells; and

identifying a test compound as a candidate drug for treating tumors if it decreases the activity of of one more TEM proteins in said cells.

72. The method of claim 72 wherein the cells are endothelial cells.

73. The method of claim 72 wherein the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more TEMs.

74. A method to identify candidate drugs for treating patients bearing tumors, comprising:

contacting a test compound with recombinant host cells which are transfected with an expession construct which encodes one or more TEM proteins selected from the group consisting of 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 40, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: 198, 202, 204, 206, 208, 210, 212, 214, 216, 218, 223 & 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 358, 257, 259, 261, 263, 267, 269, 271, 273, and 275, respectively;

determining proliferation of said cells; and

identifying a test compound which inhibits proliferation of said cells as a candidate drug for treating patients bearing tumors.

75. A method to identify candidate drugs for treating tumors, comprising:

contacting cells which express one or more NEM genes selected from the group consisting of: 14, 22, 23, and 33 as shown in SEQ ID NO: 278, 282, 284, and 288, respectively, with a test compound;

determining expression of said one or more NEM genes by hybridization of mRNA of said cells to a nucleic acid probe which is complementary to said mRNA; and

identifying a test compound as a candidate drug for treating tumors if it increases expression of said one or more NEM genes.

76. The method of claim 76 wherein the cells are endothelial cells.

77. The method of claim 76 wherein the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more NEMs.

78. A method to identify candidate drugs for treating tumors, comprising:

contacting cells which express one or more NEM proteins selected from the group consisting of: 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289, with a test compound;

determining amount of said one or more NEM proteins in said cells; and

identifying a test compound as a candidate drug for treating tumors if it increases the amount of one more NEM proteins in said cells.

79. The method of claim 79 wherein the cells are endothelial cells.

80. The method of claim 79 wherein the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more NEMs.

81. A method to identify candidate drugs for treating tumors, comprising:

contacting cells which express one or more NEM proteins selected from the group consisting of: 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289, with a test compound;

determining activity of said one or more NEM proteins in said cells; and

identifying a test compound as a candidate drug for treating tumors if it increases the activity of one more NEM proteins in said cells.

82. The method of claim 82 wherein the cells are endothelial cells.

83. The method of claim 82 wherein the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more NEMs.

84. A method to identify candidate drugs for treating patients bearing tumors, comprising:

contacting a test compound with recombinant host cells which are transfected with an expession construct which encodes one or more NEM proteins selected from the group consisting of 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289;

determining proliferation of said cells; and

identifying a test compound which stimulates proliferation of said cells as a candidate drug for treating patients bearing tumors.

85. A method for identification of a ligand involved in endothelial cell regulation, comprising:

contacting a test compound with a human transmembrane TEM protein selected from the group consisting of 1, 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 40, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: 196,

198, 202, 204, 206, 208, 210, 212, 214, 216, 218, 223 & 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 358, 257, 259, 261, 263, 267, 269, 271, 273, and 275;

determining binding of a test compound to the human transmembrane protein, wherein a test compound which binds to the protein is identified as a ligand involved in endothelial cell regulation.

86. A method of inducing an immune response in a mammal, comprising:

administering to the mammal a cell which expresses a transmembrane protein selected from the group consisting of: TEM 1, 9, 13, 17, 19, 22, 30, and 44 as shown in SEQ ID NO: 196, 212, 220, 230, 232, 238, 250 and 271 , respectively, wherein the cell is a recombinant cell which comprises a vector econding said transmembrane protein, or the cell is a fusion of a dendritic cell and a tumor endothelium cell, whereby an immune response to the human transmembrane protein is induced in the mammal.

Figure 1

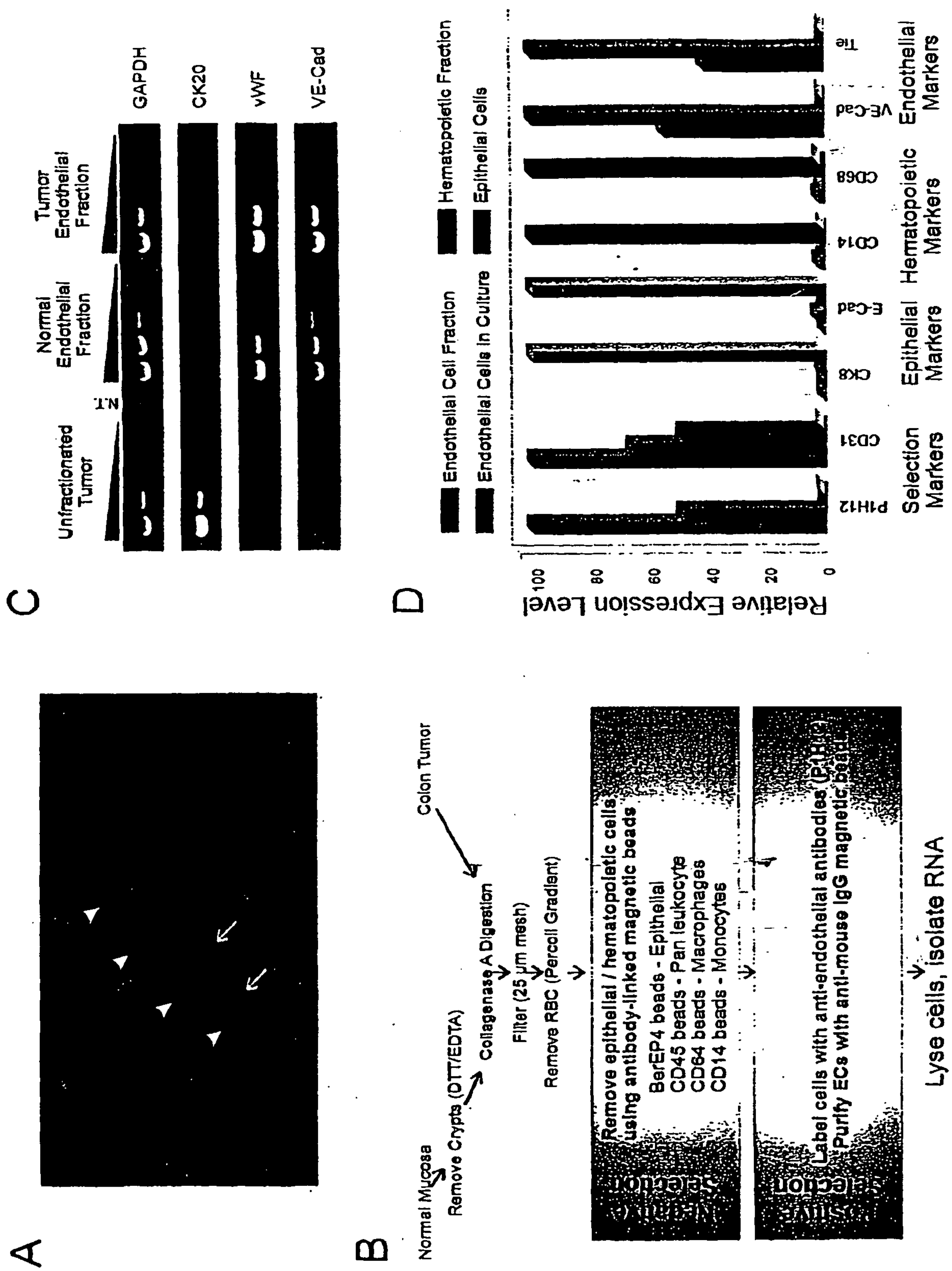

A
B
Normal Mucosa
Remove Crypts (DTT/EDTA)
Colon Tumor
Collagenase A Digestion
Filter (25 μm mesh)
Remove RBC (Percoll Gradient)
Negative Selection
Remove epithelial / hematopoietic cells using antibody-linked magnetic beads
BerEP4 beads - Epithelial
CD45 beads - Pan leukocyte
CD64 beads - Macrophages
CD14 beads - Monocytes
Positive Selection
Label cells with anti-endothelial antibodies (P1H12)
Purify ECs with anti-mouse IgG magnetic beads
Lyse cells, isolate RNA
C
Unfractionated Tumor
N.T.
Normal Endothelial Fraction
Tumor Endothelial Fraction
GAPDH
CK20
vWF
VE-Cad
D
Endothelial Cell Fraction
Endothelial Cells in Culture
Hematopoietic Fraction
Epithelial Cells
Relative Expression Level
100
80
60
40
20
0
P1H12
CD31
CK8
E-Cad
CD14
CD68
VE-Cad
Tie
Selection Markers
Epithelial Markers
Hematopoietic Markers
Endothelial Markers

Figure 2

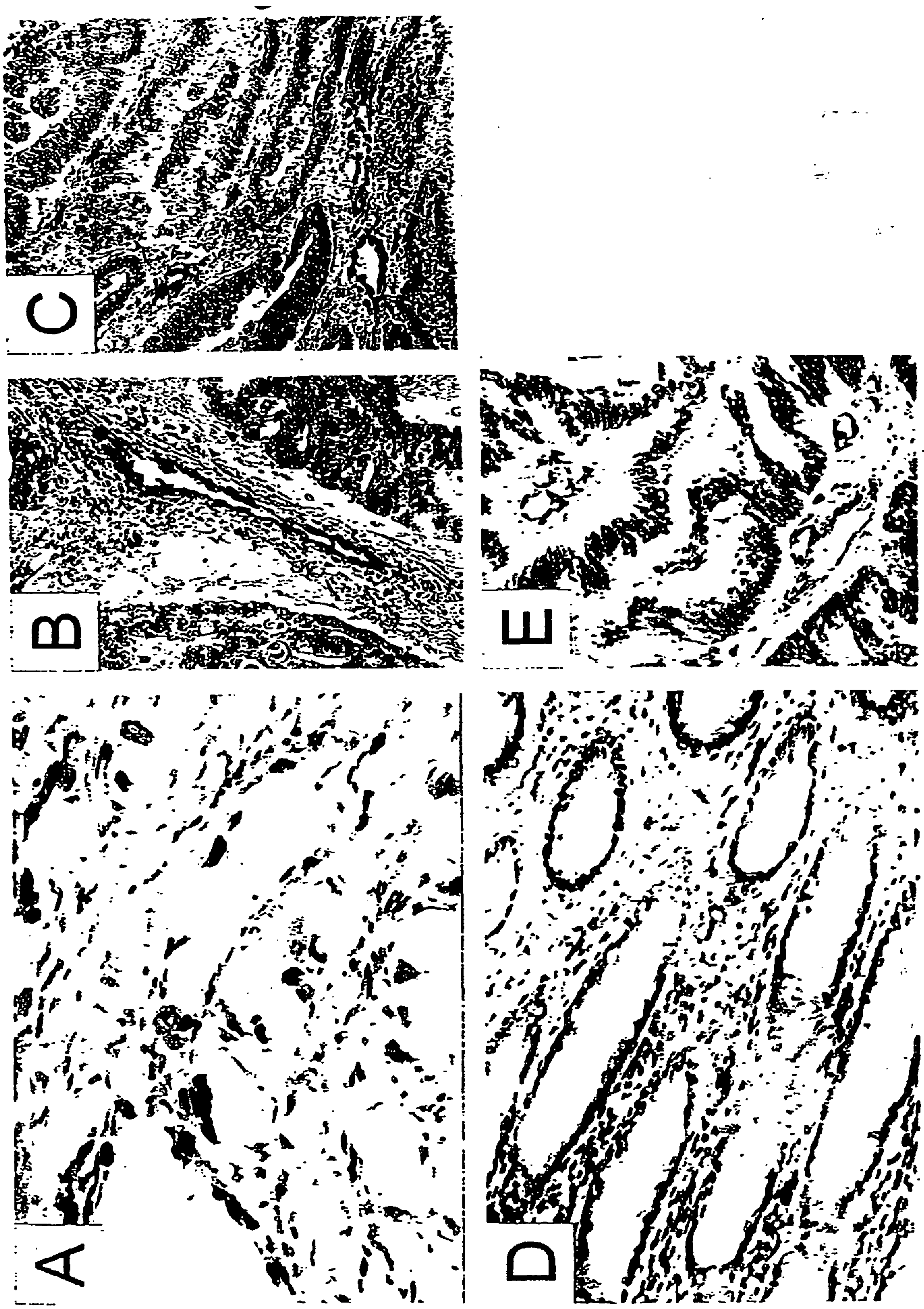
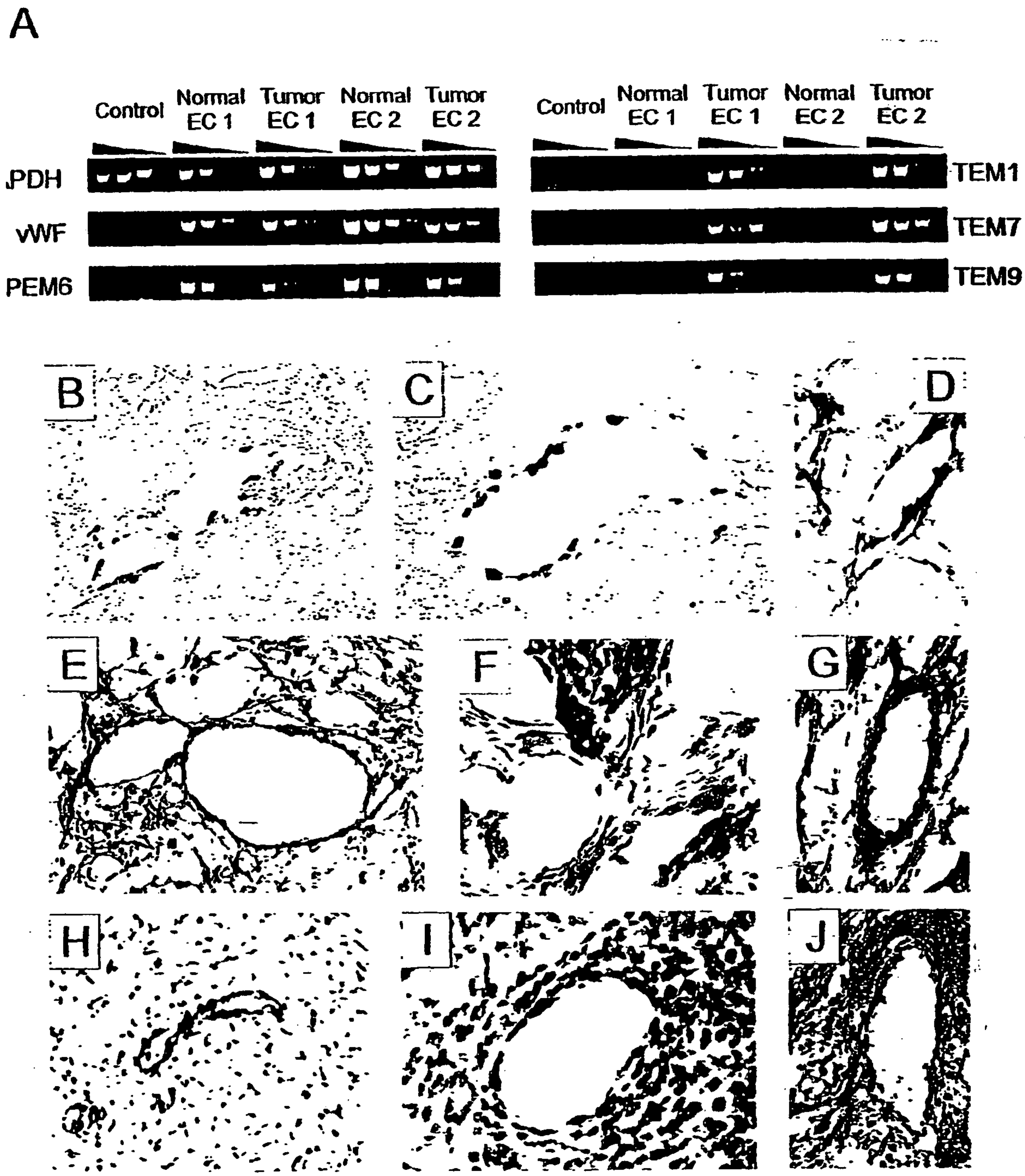


Figure 3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TEM7
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Figure 4

SEQUENCE LISTING

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Bert Vogelstein
Kenneth Kinzler

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tagaacacta ggcttcttct ttcatgtagt tcctcataag caggggccag aatatctcag    3960
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<210> 177
<211> 757
<212> PRT
<213> Homo sapiens

<400> 177
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Ser Cys Tyr Ala Leu Phe Pro Arg Arg Arg Thr Phe Leu Glu Ala Trp
35 40 45
Arg Ala Cys Arg Glu Leu Gly Gly Asp Leu Ala Thr Pro Arg Thr Pro
50 55 60
Glu Glu Ala Gln Arg Val Asp Ser Leu Val Gly Ala Gly Pro Ala Ser
65 70 75 80
Arg Leu Leu Trp Ile Gly Leu Gln Arg Gln Ala Arg Gln Cys Gln Leu
85 90 95
Gln Arg Pro Leu Arg Gly Phe Thr Trp Thr Thr Gly Asp Gln Asp Thr
100 105 110
Ala Phe Thr Asn Trp Ala Gln Pro Ala Ser Gly Gly Pro Cys Pro Ala
115 120 125
Gln Arg Cys Val Ala Leu Glu Ala Ser Gly Glu His Arg Trp Leu Glu
130 135 140
Gly Ser Cys Thr Leu Ala Val Asp Gly Tyr Leu Cys Gln Phe Gly Phe
145 150 155 160
Glu Gly Ala Cys Pro Ala Leu Gln Asp Glu Ala Gly Gln Ala Gly Pro
165 170 175
Ala Val Tyr Thr Thr Pro Phe His Leu Val Ser Thr Glu Phe Glu Trp
180 185 190
Leu Pro Phe Gly Ser Val Ala Ala Val Gln Cys Gln Ala Gly Arg Gly

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        195                 200                 205
Ala Ser Leu Leu Cys Val Lys Gln Pro Glu Gly Gly Val Gly Trp Ser
    210                 215                 220
Arg Ala Gly Pro Leu Cys Leu Gly Thr Gly Cys Ser Pro Asp Asn Gly
225                 230                 235                 240
Gly Cys Glu His Glu Cys Val Glu Glu Val Asp Gly His Val Ser Cys
                245                 250                 255
Arg Cys Thr Glu Gly Phe Arg Leu Ala Ala Asp Gly Arg Ser Cys Glu
            260                 265                 270
Asp Pro Cys Ala Gln Ala Pro Cys Glu Gln Gln Cys Glu Pro Gly Gly
        275                 280                 285
Pro Gln Gly Tyr Ser Cys His Cys Arg Leu Gly Phe Arg Pro Ala Glu
    290                 295                 300
Asp Asp Pro His Arg Cys Val Asp Thr Asp Glu Cys Gln Ile Ala Gly
305                 310                 315                 320
Val Cys Gln Gln Met Cys Val Asn Tyr Val Gly Gly Phe Glu Cys Tyr
                325                 330                 335
Cys Ser Glu Gly His Glu Leu Glu Ala Asp Gly Ile Ser Cys Ser Pro
            340                 345                 350
Ala Gly Ala Met Gly Ala Gln Ala Ser Gln Asp Leu Gly Asp Glu Leu
        355                 360                 365
Leu Asp Asp Gly Glu Asp Glu Glu Asp Glu Asp Glu Ala Trp Lys Ala
    370                 375                 380
Phe Asn Gly Gly Trp Thr Glu Met Pro Gly Ile Leu Trp Met Glu Pro
385                 390                 395                 400
Thr Gln Pro Pro Asp Phe Ala Leu Ala Tyr Arg Pro Ser Phe Pro Glu
                405                 410                 415
Asp Arg Glu Pro Gln Ile Pro Tyr Pro Glu Pro Thr Trp Pro Pro Pro
            420                 425                 430
Leu Ser Ala Pro Arg Val Pro Tyr His Ser Ser Val Leu Ser Val Thr
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Arg Pro Val Val Val Ser Ala Thr His Pro Thr Leu Pro Ser Ala His
    450                 455                 460
Gln Pro Pro Val Ile Pro Ala Thr His Pro Ala Leu Ser Arg Asp His
465                 470                 475                 480
Gln Ile Pro Val Ile Ala Ala Asn Tyr Pro Asp Leu Pro Ser Ala Tyr
                485                 490                 495
Gln Pro Gly Ile Leu Ser Val Ser His Ser Ala Gln Pro Pro Ala His
            500                 505                 510
Gln Pro Pro Met Ile Ser Thr Lys Tyr Pro Glu Leu Phe Pro Ala His
        515                 520                 525
Gln Ser Pro Met Phe Pro Asp Thr Arg Val Ala Gly Thr Gln Thr Thr
    530                 535                 540
Thr His Leu Pro Gly Ile Pro Pro Asn His Ala Pro Leu Val Thr Thr
545                 550                 555                 560
Leu Gly Ala Gln Leu Pro Pro Gln Ala Pro Asp Ala Leu Val Leu Arg
                565                 570                 575
Thr Gln Ala Thr Gln Leu Pro Ile Ile Pro Thr Ala Gln Pro Ser Leu
            580                 585                 590
Thr Thr Thr Ser Arg Ser Pro Val Ser Pro Ala His Gln Ile Ser Val
        595                 600                 605
Pro Ala Ala Thr Gln Pro Ala Ala Leu Pro Thr Leu Leu Pro Ser Gln
    610                 615                 620
Ser Pro Thr Asn Gln Thr Ser Pro Ile Ser Pro Thr His Pro His Ser
625                 630                 635                 640
Lys Ala Pro Gln Ile Pro Arg Glu Asp Gly Pro Ser Pro Lys Leu Ala
                645                 650                 655
Leu Trp Leu Pro Ser Pro Ala Pro Thr Ala Ala Pro Thr Ala Leu Gly
            660                 665                 670
Glu Ala Gly Leu Ala Glu His Ser Gln Arg Asp Asp Arg Trp Leu Leu
        675                 680                 685
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Val Ala Leu Leu Val Pro Thr Cys Val Phe Leu Val Val Leu Leu Ala
    690   695   700
Leu Gly Ile Val Tyr Cys Thr Arg Cys Gly Pro His Ala Pro Asn Lys
705   710   715   720
Arg Ile Thr Asp Cys Tyr Arg Trp Val Ile His Ala Gly Ser Lys Ser
                725   730   735
Pro Thr Glu Pro Met Pro Pro Arg Gly Ser Leu Thr Gly Val Gln Thr
            740   745   750
Cys Arg Thr Ser Val
        755

<210> 178
<211> 278
<212> PRT
<213> Homo sapiens

<400> 178
Met Pro Ala Ser Leu Ala Leu Leu Gln Pro Arg Ala Met Met Lys Thr
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Leu Ser Ser Gly Asn Cys Thr Leu Ser Val Pro Ala Lys Asn Ser Tyr
            20   25   30
Arg Met Val Val Leu Gly Ala Ser Arg Val Gly Lys Ser Ser Ile Val
        35   40   45
Ser Arg Phe Leu Asn Gly Arg Phe Glu Asp Gln Tyr Thr Pro Thr Ile
    50   55   60
Glu Asp Phe His Arg Lys Val Tyr Asn Ile Arg Gly Asp Met Tyr Gln
65   70   75   80
Leu Asp Ile Leu Asp Thr Ser Gly Asn His Pro Phe Pro Ala Met Arg
                85   90   95
Arg Leu Ser Ile Leu Thr Gly Asp Val Phe Ile Leu Val Phe Ser Leu
            100   105   110
Asp Asn Arg Glu Ser Phe Asp Glu Val Lys Arg Leu Gln Lys Gln Ile
        115   120   125
Leu Glu Val Lys Ser Cys Leu Lys Asn Lys Thr Lys Glu Ala Ala Glu
    130   135   140
Leu Pro Met Val Ile Cys Gly Asn Lys Asn Asp His Gly Glu Leu Cys
145   150   155   160
Arg Gln Val Pro Thr Thr Glu Ala Glu Leu Leu Val Ser Gly Asp Glu
                165   170   175
Asn Cys Ala Tyr Phe Glu Val Ser Ala Lys Lys Asn Thr Asn Val Asp
            180   185   190
Glu Met Phe Tyr Val Leu Phe Ser Met Ala Lys Leu Pro His Glu Met
        195   200   205
Ser Pro Ala Leu His Arg Lys Ile Ser Val Gln Tyr Gly Asp Ala Phe
    210   215   220
His Pro Arg Pro Phe Cys Met Arg Arg Val Lys Glu Met Asp Ala Tyr
225   230   235   240
Gly Met Val Ser Pro Phe Ala Arg Arg Pro Ser Val Asn Ser Asp Leu
                245   250   255
Lys Tyr Ile Lys Ala Lys Val Leu Arg Glu Gly Gln Ala Arg Glu Arg
            260   265   270
Asp Lys Cys Thr Ile Gln
        275

<210> 179
<211> 1002
<212> PRT
<213> Homo sapiens

<400> 179
Met Arg Gly Glu Leu Trp Leu Leu Val Leu Val Leu Arg Glu Ala Ala

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Ser Gly Trp Ala Ala Lys Gly Thr Val Arg Gly Trp Asn Arg Arg Ala
        35                  40                  45
Arg Glu Ser Pro Gly His Val Ser Glu Pro Asp Arg Thr Gln Leu Ser
    50                  55                  60
Gln Asp Leu Gly Gly Gly Thr Leu Ala Met Asp Thr Leu Pro Asp Asn
65                  70                  75                  80
Arg Thr Arg Val Val Glu Asp Asn His Ser Tyr Tyr Val Ser Arg Leu
                85                  90                  95
Tyr Gly Pro Ser Glu Pro His Ser Arg Glu Leu Trp Val Asp Val Ala
            100                 105                 110
Glu Ala Asn Arg Ser Gln Val Lys Ile His Thr Ile Leu Ser Asn Thr
        115                 120                 125
His Arg Gln Ala Ser Arg Val Val Leu Ser Phe Asp Phe Pro Phe Tyr
    130                 135                 140
Gly His Pro Leu Arg Gln Ile Thr Ile Ala Thr Gly Gly Phe Ile Phe
145                 150                 155                 160
Met Gly Asp Val Ile His Arg Met Leu Thr Ala Thr Gln Tyr Val Ala
                165                 170                 175
Pro Leu Met Ala Asn Phe Asn Pro Gly Tyr Ser Asp Asn Ser Thr Val
            180                 185                 190
Val Tyr Phe Asp Asn Gly Thr Val Phe Val Val Gln Trp Asp His Val
        195                 200                 205
Tyr Leu Gln Gly Trp Glu Asp Lys Gly Ser Phe Thr Phe Gln Ala Ala
    210                 215                 220
Leu His His Asp Gly Arg Ile Val Phe Ala Tyr Lys Glu Ile Pro Met
225                 230                 235                 240
Ser Val Pro Glu Ile Ser Ser Ser Gln His Pro Val Lys Thr Gly Leu
                245                 250                 255
Ser Asp Ala Phe Met Ile Leu Asn Pro Ser Pro Asp Val Pro Glu Ser
            260                 265                 270
Arg Arg Arg Ser Ile Phe Glu Tyr His Arg Ile Glu Leu Asp Pro Ser
        275                 280                 285
Lys Val Thr Ser Met Ser Ala Val Glu Phe Thr Pro Leu Pro Thr Cys
    290                 295                 300
Leu Gln His Arg Ser Cys Asp Ala Cys Met Ser Ser Asp Leu Thr Phe
305                 310                 315                 320
Asn Cys Ser Trp Cys His Val Leu Gln Arg Cys Ser Ser Gly Phe Asp
                325                 330                 335
Arg Tyr Arg Gln Glu Trp Asp Gly Thr Met Gly Cys Ala Gln Glu Ala
            340                 345                 350
Glu Gly Gln Asp Val Arg Gly Leu Pro Gly Met Arg Thr Thr Thr Ser
        355                 360                 365
Ala Ser Pro Asp Thr Ser Phe Ser Pro Tyr Asp Gly Asp Leu Thr Thr
    370                 375                 380
Thr Ser Ser Ser Leu Phe Ile Asp Ser Leu Thr Thr Glu Asp Asp Thr
385                 390                 395                 400
Lys Leu Asn Pro Tyr Ala Gly Gly Asp Gly Leu Gln Asn Asn Leu Ser
                405                 410                 415
Pro Lys Thr Lys Gly Thr Pro Val His Leu Gly Thr Ile Val Gly Ile
            420                 425                 430
Val Leu Ala Val Leu Leu Val Ala Ala Ile Ile Leu Ala Gly Ile Tyr
        435                 440                 445
Ile Asn Gly His Pro Thr Ser Asn Ala Ala Leu Phe Phe Ile Glu Arg
    450                 455                 460
Arg Pro His His Trp Pro Ala Met Lys Phe Arg Ser His Pro Asp His
465                 470                 475                 480
Ser Thr Tyr Ala Glu Val Glu Pro Ser Gly His Glu Lys Glu Gly Phe
                485                 490                 495
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Met Glu Ala Glu Gln Cys Met Arg Gly Glu Leu Trp Leu Leu Val Leu
500 505 510
Val Leu Arg Glu Ala Ala Arg Ala Leu Ser Pro Gln Pro Gly Ala Gly
515 520 525
His Asp Glu Gly Pro Gly Ser Gly Trp Ala Ala Lys Gly Thr Val Arg
530 535 540
Gly Trp Asn Arg Arg Ala Arg Glu Ser Pro Gly His Val Ser Glu Pro
545 550 555 560
Asp Arg Thr Gln Leu Ser Gln Asp Leu Gly Gly Gly Thr Leu Ala Met
565 570 575
Asp Thr Leu Pro Asp Asn Arg Thr Arg Val Val Glu Asp Asn His Ser
580 585 590
Tyr Tyr Val Ser Arg Leu Tyr Gly Pro Ser Glu Pro His Ser Arg Glu
595 600 605
Leu Trp Val Asp Val Ala Glu Ala Asn Arg Ser Gln Val Lys Ile His
610 615 620
Thr Ile Leu Ser Asn Thr His Arg Gln Ala Ser Arg Val Val Leu Ser
625 630 635 640
Phe Asp Phe Pro Phe Tyr Gly His Pro Leu Arg Gln Ile Thr Ile Ala
645 650 655
Thr Gly Gly Phe Ile Phe Met Gly Asp Val Ile His Arg Met Leu Thr
660 665 670
Ala Thr Gln Tyr Val Ala Pro Leu Met Ala Asn Phe Asn Pro Gly Tyr
675 680 685
Ser Asp Asn Ser Thr Val Val Tyr Phe Asp Asn Gly Thr Val Phe Val
690 695 700
Val Gln Trp Asp His Val Tyr Leu Gln Gly Trp Glu Asp Lys Gly Ser
705 710 715 720
Phe Thr Phe Gln Ala Ala Leu His His Asp Gly Arg Ile Val Phe Ala
725 730 735
Tyr Lys Glu Ile Pro Met Ser Val Pro Glu Ile Ser Ser Ser Gln His
740 745 750
Pro Val Lys Thr Gly Leu Ser Asp Ala Phe Met Ile Leu Asn Pro Ser
755 760 765
Pro Asp Val Pro Glu Ser Arg Arg Arg Ser Ile Phe Glu Tyr His Arg
770 775 780
Ile Glu Leu Asp Pro Ser Lys Val Thr Ser Met Ser Ala Val Glu Phe
785 790 795 800
Thr Pro Leu Pro Thr Cys Leu Gln His Arg Ser Cys Asp Ala Cys Met
805 810 815
Ser Ser Asp Leu Thr Phe Asn Cys Ser Trp Cys His Val Leu Gln Arg
820 825 830
Cys Ser Ser Gly Phe Asp Arg Tyr Arg Gln Glu Trp Met Asp Tyr Gly
835 840 845
Cys Ala Gln Glu Ala Glu Gly Arg Met Cys Glu Asp Phe Gln Asp Glu
850 855 860
Asp His Asp Ser Ala Ser Pro Asp Thr Ser Phe Ser Pro Tyr Asp Gly
865 870 875 880
Asp Leu Thr Thr Thr Ser Ser Ser Leu Phe Ile Asp Ser Leu Thr Thr
885 890 895
Glu Asp Asp Thr Lys Leu Asn Pro Tyr Ala Gly Gly Asp Gly Leu Gln
900 905 910
Asn Asn Leu Ser Pro Lys Thr Lys Gly Thr Pro Val His Leu Gly Thr
915 920 925
Ile Val Gly Ile Val Leu Ala Val Leu Leu Val Ala Ala Ile Ile Leu
930 935 940
Ala Gly Ile Tyr Ile Asn Gly His Pro Thr Ser Asn Ala Ala Leu Phe
945 950 955 960
Phe Ile Glu Arg Arg Pro His His Trp Pro Ala Met Lys Phe Arg Ser
965 970 975
His Pro Asp His Ser Thr Tyr Ala Glu Val Glu Pro Ser Gly His Glu

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<210> 180
<211> 5680
<212> DNA
<213> Homo sapiens

<400> 180
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<212> PRT
<213> Homo sapiens

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35 40 45
Leu Asp Lys Ser Gly Ser Val Leu His His Trp Asn Glu Ile Tyr Tyr
50 55 60
Phe Val Glu Gln Leu Ala His Lys Phe Ile Ser Pro Gln Leu Arg Met
65 70 75 80
Ser Phe Ile Val Phe Ser Thr Arg Gly Thr Thr Leu Met Lys Leu Thr
85 90 95
Glu Asp Arg Glu Gln Ile Arg Gln Gly Leu Glu Glu Leu Gln Lys Val
100 105 110
Leu Pro Gly Gly Asp Thr Tyr Met His Glu Gly Phe Glu Arg Ala Ser
115 120 125
Glu Gln Ile Tyr Tyr Glu Asn Arg Gln Gly Tyr Arg Thr Ala Ser Val
130 135 140
Ile Ile Ala Leu Thr Asp Gly Glu Leu His Glu Asp Leu Phe Phe Tyr
145 150 155 160
Ser Glu Arg Glu Ala Asn Arg Ser Arg Asp Leu Gly Ala Ile Val Tyr
165 170 175
Cys Val Gly Val Lys Asp Phe Asn Glu Thr Gln Leu Ala Arg Ile Ala
180 185 190
Asp Ser Lys Asp His Val Phe Pro Val Asn Asp Gly Phe Gln Ala Leu
195 200 205
Gln Gly Ile Ile His Ser Ile Leu Lys Lys Ser Cys Ile Glu Ile Leu
210 215 220
Ala Ala Glu Pro Ser Thr Ile Cys Ala Gly Glu Ser Phe Gln Val Val
225 230 235 240
Val Arg Gly Asn Gly Phe Arg His Ala Arg Asn Val Asp Arg Val Leu
245 250 255
Cys Ser Phe Lys Ile Asn Asp Ser Val Thr Leu Asn Glu Lys Pro Phe
260 265 270
Ser Val Glu Asp Thr Tyr Leu Leu Cys Pro Ala Pro Ile Leu Lys Glu
275 280 285
Val Gly Met Lys Ala Ala Leu Gln Val Ser Met Asn Asp Gly Leu Ser
290 295 300
Phe Ile Ser Ser Ser Val Ile Ile Thr Thr Thr His Cys Ser Asp Gly
305 310 315 320
Ser Ile Leu Ala Ile Ala Leu Leu Ile Leu Phe Leu Leu Leu Ala Leu
325 330 335
Ala Leu Leu Trp Trp Phe Trp Pro Leu Cys Cys Thr Val Ile Ile Lys
340 345 350
Glu Val Pro Pro Pro Pro Ala Glu Glu Ser Glu Glu Glu Asp Asp Asp
355 360 365
Gly Leu Pro Lys Lys Lys Trp Pro Thr Val Asp Ala Ser Tyr Tyr Gly

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Arg Val Lys Met Pro Glu Gln Glu Tyr Glu Phe Pro Glu Pro Arg Asn
            420                 425                 430
Leu Asn Asn Asn Met Arg Arg Pro Ser Ser Pro Arg Lys Trp Tyr Ser
        435                 440                 445
Pro Ile Lys Gly Lys Leu Asp Ala Leu Trp Val Leu Leu Arg Lys Gly
    450                 455                 460
Tyr Asp Arg Val Ser Val Met Arg Pro Gln Pro Gly Asp Thr Gly Arg
465                 470                 475                 480
Cys Ile Asn Phe Thr Arg Val Lys Asn Asn Gln Pro Ala Lys Tyr Pro
                485                 490                 495
Leu Asn Asn Ala Tyr His Thr Ser Ser Pro Pro Pro Ala Pro Ile Tyr
            500                 505                 510
Thr Pro Pro Pro Pro Ala Pro His Cys Pro Pro Pro Pro Pro Ser Ala
        515                 520                 525
Pro Thr Pro Pro Ile Pro Ser Pro Pro Ser Thr Leu Pro Pro Pro Pro
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Ser Ile Arg Ser Cys Lys Cys Ser Gly Glu Arg Pro Lys Gly Leu Ser
        35                  40                  45
Gly Gly Val Pro Gly Pro Ala Arg Arg Arg Val Val Cys Ser Gly Gly
    50                  55                  60
Asp Leu Pro Glu Pro Pro Glu Pro Gly Leu Leu Pro Asn Gly Thr Val
65                  70                  75                  80
Thr Leu Leu Leu Ser Asn Asn Lys Ile Thr Gly Leu Arg Asn Gly Ser
                85                  90                  95
Phe Leu Gly Leu Ser Leu Leu Glu Lys Leu Asp Leu Arg Asn Asn Ile
            100                 105                 110
Ile Ser Thr Val Gln Pro Gly Ala Phe Leu Gly Leu Gly Glu Leu Lys
        115                 120                 125
Arg Leu Asp Leu Ser Asn Asn Arg Ile Gly Cys Leu Thr Ser Glu Thr
    130                 135                 140
Phe Gln Gly Leu Pro Arg Leu Leu Arg Leu Asn Ile Ser Gly Asn Ile
145                 150                 155                 160
Phe Ser Ser Leu Gln Pro Gly Val Phe Asp Glu Leu Pro Ala Leu Lys
                165                 170                 175
Val Val Asp Leu Gly Thr Glu Phe Leu Thr Cys Asp Cys His Leu Arg
            180                 185                 190
Trp Leu Leu Pro Trp Ala Gln Asn Arg Ser Leu Gln Leu Ser Glu His
        195                 200                 205
Thr Leu Cys Ala Tyr Pro Ser Ala Leu His Ala Gln Ala Leu Gly Ser
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Leu Gln Glu Ala Gln Leu Cys Cys Glu Gly Ala Leu Glu Leu His Thr
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His His Leu Ile Pro Ser Leu Arg Gln Val Val Phe Gln Gly Asp Arg
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Leu Pro Phe Gln Cys Ser Ala Ser Tyr Leu Gly Asn Asp Thr Arg Ile
            260                 265                 270
Arg Trp Tyr His Asn Arg Ala Pro Val Glu Gly Asp Glu Gln Ala Gly
        275                 280                 285
Ile Leu Leu Ala Glu Ser Leu Ile His Asp Cys Thr Phe Ile Thr Ser
    290                 295                 300
Glu Leu Thr Leu Ser His Ile Gly Val Trp Ala Ser Gly Glu Trp Glu
305                 310                 315                 320
Cys Thr Val Ser Met Ala Gln Gly Asn Ala Ser Lys Lys Val Glu Ile
                325                 330                 335
Val Val Leu Glu Thr Ser Ala Ser Tyr Cys Pro Ala Glu Arg Val Ala
            340                 345                 350
Asn Asn Arg Gly Asp Phe Arg Trp Pro Arg Thr Leu Ala Gly Ile Thr
        355                 360                 365
Ala Tyr Gln Ser Cys Leu Gln Tyr Pro Phe Thr Ser Val Pro Leu Gly
    370                 375                 380
Gly Gly Ala Pro Gly Thr Arg Ala Ser Arg Arg Cys Asp Arg Ala Gly
385                 390                 395                 400
Arg Trp Glu Pro Gly Asp Tyr Ser His Cys Leu Tyr Thr Asn Asp Ile
                405                 410                 415
Thr Arg Val Leu Tyr Thr Phe Val Leu Met Pro Ile Asn Ala Ser Asn
            420                 425                 430
Ala Leu Thr Leu Ala His Gln Leu Arg Val Tyr Thr Ala Glu Ala Ala
        435                 440                 445
Ser Phe Ser Asp Met Met Asp Val Val Tyr Val Ala Gln Met Ile Gln
    450                 455                 460
Lys Phe Leu Gly Tyr Val Asp Gln Ile Lys Glu Leu Val Glu Val Met
465                 470                 475                 480
Val Asp Met Ala Ser Asn Leu Met Leu Val Asp Glu His Leu Leu Trp
                485                 490                 495
Leu Ala Gln Arg Glu Asp Lys Ala Cys Ser Arg Ile Val Gly Ala Leu
            500                 505                 510
Glu Arg Ile Gly Gly Ala Ala Leu Ser Pro His Ala Gln His Ile Ser
        515                 520                 525
Val Asn Ala Arg Asn Val Ala Leu Glu Ala Tyr Leu Ile Lys Pro His
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Ser Tyr Val Gly Leu Thr Cys Thr Ala Phe Gln Arg Arg Glu Gly Gly
545                 550                 555                 560
Val Pro Gly Thr Arg Pro Gly Ser Pro Gly Gln Asn Pro Pro Pro Glu
                565                 570                 575
Pro Glu Pro Pro Ala Asp Gln Gln Leu Arg Phe Arg Cys Thr Thr Gly
            580                 585                 590
Arg Pro Asn Val Ser Leu Ser Ser Phe His Ile Lys Asn Ser Val Ala
        595                 600                 605
Leu Ala Ser Ile Gln Leu Pro Pro Ser Leu Phe Ser Ser Leu Pro Ala
    610                 615                 620
Ala Leu Ala Pro Pro Val Pro Pro Asp Cys Thr Leu Gln Leu Leu Val
625                 630                 635                 640
Phe Arg Asn Gly Arg Leu Phe His Ser His Ser Asn Thr Ser Arg Pro
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Gly Ala Ala Gly Pro Gly Lys Arg Arg Gly Val Ala Thr Pro Val Ile
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Phe Ala Gly Thr Ser Gly Cys Gly Val Gly Asn Leu Thr Glu Pro Val
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Ala Val Ser Leu Arg His Trp Ala Glu Gly Ala Glu Pro Val Ala Ala
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Trp Trp Ser Gln Glu Gly Pro Gly Glu Ala Gly Gly Trp Thr Ser Glu
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Gln His Leu Gly Asn Val Ala Val Leu Met Glu Leu Ser Ala Phe Pro
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Arg Glu Val Gly Gly Ala Gly Ala Gly Leu His Pro Val Val Tyr Pro
        755                 760                 765
Cys Thr Ala Leu Leu Leu Leu Cys Leu Phe Ala Thr Ile Ile Thr Tyr
    770                 775                 780
Ile Leu Asn His Ser Ser Ile Arg Val Ser Arg Lys Gly Trp His Met
785                 790                 795                 800
Leu Leu Asn Leu Cys Phe His Ile Ala Met Thr Ser Ala Val Phe Ala
                805                 810                 815
Gly Gly Ile Thr Leu Thr Asn Tyr Gln Met Val Cys Gln Ala Val Gly
            820                 825                 830
Ile Thr Leu His Tyr Ser Ser Leu Ser Thr Leu Leu Trp Met Gly Val
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Lys Ala Arg Val Leu His Lys Glu Leu Thr Trp Arg Ala Pro Pro Pro
    850                 855                 860
Gln Glu Gly Asp Pro Ala Leu Pro Thr Pro Ser Pro Met Leu Arg Phe
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Tyr Leu Ile Ala Gly Gly Ile Pro Leu Ile Ile Cys Gly Ile Thr Ala
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Ala Val Asn Ile His Asn Tyr Arg Asp His Ser Pro Tyr Cys Trp Leu
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Val Trp Arg Pro Ser Leu Gly Ala Phe Tyr Ile Pro Val Ala Leu Ile
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Leu Leu Ile Thr Trp Ile Tyr Phe Leu Cys Ala Gly Leu Arg Leu Arg
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Gly Pro Leu Ala Gln Asn Pro Lys Ala Gly Asn Ser Arg Ala Ser Leu
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Glu Ala Gly Glu Glu Leu Arg Gly Ser Thr Arg Leu Arg Gly Ser Gly
                965                 970                 975
Pro Leu Leu Ser Asp Ser Gly Ser Leu Leu Ala Thr Gly Ser Ala Arg
            980                 985                 990
Val Gly Thr Pro Gly Pro Pro Glu Asp Gly Asp Ser Leu Tyr Ser Pro
        995                 1000                1005
Gly Val Gln Leu Gly Ala Leu Val Thr Thr His Phe Leu Tyr Leu Ala
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Met Trp Ala Cys Gly Ala Leu Ala Val Ser Gln Arg Trp Leu Pro Arg
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Val Val Cys Ser Cys Leu Tyr Gly Val Ala Ala Ser Ala Leu Gly Leu
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Phe Val Phe Thr His His Cys Ala Arg Arg Arg Asp Val Arg Ala Ser
            1060                1065                1070
Trp Arg Ala Cys Cys Pro Pro Ala Ser Pro Ala Ala Pro His Ala Pro
        1075                1080                1085
Pro Arg Ala Leu Pro Ala Ala Ala Glu Asp Gly Ser Pro Val Phe Gly
    1090                1095                1100
Glu Gly Pro Pro Ser Leu Lys Ser Ser Pro Ser Gly Ser Ser Gly His
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Pro Leu Ala Leu Gly Pro Cys Lys Leu Thr Asn Leu Gln Leu Ala Gln
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Ser Gln Val Cys Glu Ala Gly Ala Ala Ala Gly Gly Glu Gly Glu Pro
            1140                1145                1150
Glu Pro Ala Gly Thr Arg Gly Asn Leu Ala His Arg His Pro Asn Asn
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Val His His Gly Arg Arg Ala His Lys Ser Arg Ala Lys Gly His Arg
    1170                1175                1180
Ala Gly Glu Ala Cys Gly Lys Asn Arg Leu Lys Ala Leu Arg Gly Gly
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Lys Glu Ser His Arg Arg Ser Tyr Pro Leu Asn Ala Ala Ser Leu Asn
1285 1290 1295
Gly Ala Pro Lys Gly Gly Lys Tyr Asp Asp Val Thr Leu Met Gly Ala
1300 1305 1310
Glu Val Ala Ser Gly Gly Cys Met Lys Thr Gly Leu Trp Lys Ser Glu
1315 1320 1325
Thr Thr Val
1330

<210> 189
<211> 529
<212> PRT
<213> Homo sapiens

<400> 189
Met Ala Arg Phe Pro Lys Ala Asp Leu Ala Ala Ala Gly Val Met Leu
1 5 10 15
Leu Cys His Phe Phe Thr Asp Gln Phe Gln Phe Ala Asp Gly Lys Pro
20 25 30
Gly Asp Gln Ile Leu Asp Trp Gln Tyr Gly Val Thr Gln Ala Phe Pro
35 40 45
His Thr Glu Glu Glu Val Glu Val Asp Ser His Ala Tyr Ser His Arg
50 55 60
Trp Lys Arg Asn Leu Asp Phe Leu Lys Ala Val Asp Thr Asn Arg Ala
65 70 75 80
Ser Val Gly Gln Asp Ser Pro Glu Pro Arg Ser Phe Thr Asp Leu Leu
85 90 95
Leu Asp Asp Gly Gln Asp Asn Asn Thr Gln Ile Glu Glu Asp Thr Asp
100 105 110
His Asn Tyr Tyr Ile Ser Arg Ile Tyr Gly Pro Ser Asp Ser Ala Ser
115 120 125
Arg Asp Leu Trp Val Asn Ile Asp Gln Met Glu Lys Asp Lys Val Lys
130 135 140
Ile His Gly Ile Leu Ser Asn Thr His Arg Gln Ala Ala Arg Val Asn
145 150 155 160
Leu Ser Phe Asp Phe Pro Phe Tyr Gly His Phe Leu Arg Glu Ile Thr
165 170 175
Val Ala Thr Gly Gly Phe Ile Tyr Thr Gly Glu Val Val His Arg Met
180 185 190
Leu Thr Ala Thr Gln Tyr Ile Ala Pro Leu Met Ala Asn Phe Asp Pro
195 200 205
Ser Val Ser Arg Asn Ser Thr Val Arg Tyr Phe Asp Asn Gly Thr Ala
210 215 220
Leu Val Val Gln Trp Asp His Val His Leu Gln Asp Asn Tyr Asn Leu
225 230 235 240
Gly Ser Phe Thr Phe Gln Ala Thr Leu Leu Met Asp Gly Arg Ile Ile
245 250 255
Phe Gly Tyr Lys Glu Ile Pro Val Leu Val Thr Gln Ile Ser Ser Thr
260 265 270
Asn His Pro Val Lys Val Gly Leu Ser Asp Ala Phe Val Val Val His
275 280 285
Arg Ile Gln Gln Ile Pro Asn Val Arg Arg Arg Thr Ile Tyr Glu Tyr

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    290                 295                 300
His Arg Val Glu Leu Gln Met Ser Lys Ile Thr Asn Ile Ser Ala Val
305                 310                 315                 320
Glu Met Thr Pro Leu Pro Thr Cys Leu Gln Phe Asn Arg Cys Gly Pro
                325                 330                 335
Cys Val Ser Ser Gln Ile Gly Phe Asn Cys Ser Trp Cys Ser Lys Leu
            340                 345                 350
Gln Arg Cys Ser Ser Gly Phe Asp Arg His Arg Gln Asp Trp Val Asp
        355                 360                 365
Ser Gly Cys Pro Glu Glu Ser Lys Glu Lys Met Cys Glu Asn Thr Glu
    370                 375                 380
Pro Val Glu Thr Ser Ser Arg Thr Thr Thr Thr Ile Gly Ala Thr Thr
385                 390                 395                 400
Thr Gln Phe Arg Val Leu Thr Thr Thr Arg Arg Ala Val Thr Ser Gln
                405                 410                 415
Phe Pro Thr Ser Leu Pro Thr Glu Asp Asp Thr Lys Ile Ala Leu His
            420                 425                 430
Leu Lys Asp Asn Gly Ala Ser Thr Asp Asp Ser Ala Ala Glu Lys Lys
        435                 440                 445
Gly Gly Thr Leu His Ala Gly Leu Ile Val Gly Ile Leu Ile Leu Val
    450                 455                 460
Leu Ile Val Ala Thr Ala Ile Leu Val Thr Val Tyr Met Tyr His His
465                 470                 475                 480
Pro Thr Ser Ala Ala Ser Ile Phe Phe Ile Glu Arg Arg Pro Ser Arg
                485                 490                 495
Trp Pro Ala Met Lys Phe Arg Arg Gly Ser Gly His Pro Ala Tyr Ala
            500                 505                 510
Glu Val Glu Pro Val Gly Glu Lys Glu Gly Phe Ile Val Ser Glu Gln
        515                 520                 525
Cys


      <210> 190
      <211> 765
      <212> PRT
      <213> Mus musculus

      <400> 190
Met Leu Leu Arg Leu Leu Leu Ala Trp Val Ala Ala Val Pro Ala Leu
 1               5                  10                  15
Gly Gln Val Pro Trp Thr Pro Glu Pro Arg Ala Ala Cys Gly Pro Ser
            20                  25                  30
Ser Cys Tyr Ala Leu Phe Pro Arg Arg Arg Thr Phe Leu Glu Ala Trp
        35                  40                  45
Arg Ala Cys Arg Glu Leu Gly Gly Asn Leu Ala Thr Pro Arg Thr Pro
    50                  55                  60
Glu Glu Ala Gln Arg Val Asp Ser Leu Val Gly Val Gly Pro Ala Asn
65                  70                  75                  80
Gly Leu Leu Trp Ile Gly Leu Gln Arg Gln Ala Arg Gln Cys Gln Pro
                85                  90                  95
Gln Arg Pro Leu Arg Gly Phe Ile Trp Thr Thr Gly Asp Gln Asp Thr
            100                 105                 110
Ala Phe Thr Asn Trp Ala Gln Pro Ala Thr Glu Gly Pro Cys Pro Ala
        115                 120                 125
Gln Arg Cys Ala Ala Leu Glu Ala Ser Gly Glu His Arg Trp Leu Glu
    130                 135                 140
Gly Ser Cys Thr Leu Ala Val Asp Gly Tyr Leu Cys Gln Phe Gly Phe
145                 150                 155                 160
Glu Gly Ala Cys Pro Ala Leu Pro Leu Glu Val Gly Gln Ala Gly Pro
                165                 170                 175
Ala Val Tyr Thr Thr Pro Phe Asn Leu Val Ser Ser Glu Phe Glu Trp
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        180                 185                 190
Leu Pro Phe Gly Ser Val Ala Ala Val Gln Cys Gln Ala Gly Arg Gly
    195                 200                 205
Ala Ser Leu Leu Cys Val Lys Gln Pro Ser Gly Gly Val Gly Trp Ser
    210                 215                 220
Gln Thr Gly Pro Leu Cys Pro Gly Thr Gly Cys Gly Pro Asp Asn Gly
225                 230                 235                 240
Gly Cys Glu His Glu Cys Val Glu Glu Val Asp Gly Ala Val Ser Cys
                245                 250                 255
Arg Cys Ser Glu Gly Phe Arg Leu Ala Ala Asp Gly His Ser Cys Glu
            260                 265                 270
Asp Pro Cys Ala Gln Ala Pro Cys Glu Gln Gln Cys Glu Pro Gly Gly
        275                 280                 285
Pro Gln Gly Tyr Ser Cys His Cys Arg Leu Gly Phe Arg Pro Ala Glu
    290                 295                 300
Asp Asp Pro His Arg Cys Val Asp Thr Asp Glu Cys Gln Ile Ala Gly
305                 310                 315                 320
Val Cys Gln Gln Met Cys Val Asn Tyr Val Gly Gly Phe Glu Cys Tyr
                325                 330                 335
Cys Ser Glu Gly His Glu Leu Glu Ala Asp Gly Ile Ser Cys Ser Pro
            340                 345                 350
Ala Gly Ala Met Gly Ala Gln Ala Ser Gln Asp Leu Arg Asp Glu Leu
        355                 360                 365
Leu Asp Asp Gly Glu Glu Gly Glu Asp Glu Glu Glu Pro Trp Glu Asp
    370                 375                 380
Phe Asp Gly Thr Trp Thr Glu Glu Gln Gly Ile Leu Trp Leu Ala Pro
385                 390                 395                 400
Thr His Pro Pro Asp Phe Gly Leu Pro Tyr Arg Pro Asn Phe Pro Gln
                405                 410                 415
Asp Gly Glu Pro Gln Arg Leu His Leu Glu Pro Thr Trp Pro Pro Pro
            420                 425                 430
Leu Ser Ala Pro Arg Gly Pro Tyr His Ser Ser Val Val Ser Ala Thr
        435                 440                 445
Arg Pro Met Val Ile Ser Ala Thr Arg Pro Thr Leu Pro Ser Ala His
    450                 455                 460
Lys Thr Ser Val Ile Ser Ala Thr Arg Pro Pro Leu Ser Pro Val His
465                 470                 475                 480
Pro Pro Ala Met Ala Pro Ala Thr Pro Pro Ala Val Phe Ser Glu His
                485                 490                 495
Gln Ile Pro Lys Ile Lys Ala Asn Tyr Pro Asp Leu Pro Phe Gly His
            500                 505                 510
Lys Pro Gly Ile Thr Ser Ala Thr His Pro Ala Arg Ser Pro Pro Tyr
        515                 520                 525
Gln Pro Pro Ile Ile Ser Thr Asn Tyr Pro Gln Val Phe Pro Pro His
    530                 535                 540
Gln Ala Pro Met Ser Pro Asp Thr His Thr Ile Thr Tyr Leu Pro Pro
545                 550                 555                 560
Val Pro Pro His Leu Asp Pro Gly Asp Thr Thr Ser Lys Ala His Gln
                565                 570                 575
His Pro Leu Leu Pro Asp Ala Pro Gly Ile Arg Thr Gln Ala Pro Gln
            580                 585                 590
Leu Ser Val Ser Ala Leu Gln Pro Pro Leu Pro Thr Asn Ser Arg Ser
        595                 600                 605
Ser Val His Glu Thr Pro Val Pro Ala Ala Asn Gln Pro Pro Ala Phe
    610                 615                 620
Pro Ser Ser Pro Leu Pro Pro Gln Arg Pro Thr Asn Gln Thr Ser Ser
625                 630                 635                 640
Ile Ser Pro Thr His Ser Tyr Ser Arg Ala Pro Leu Val Pro Arg Glu
                645                 650                 655
Gly Val Pro Ser Pro Lys Ser Val Pro Gln Leu Pro Ser Val Pro Ser
            660                 665                 670
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Thr Ala Ala Pro Thr Ala Leu Ala Glu Ser Gly Leu Ala Gly Gln Ser
675 680 685
Gln Arg Asp Asp Arg Trp Leu Leu Val Ala Leu Leu Val Pro Thr Cys
690 695 700
Val Phe Leu Val Val Leu Leu Ala Leu Gly Ile Val Tyr Cys Thr Arg
705 710 715 720
Cys Gly Ser His Ala Pro Asn Lys Arg Ile Thr Asp Cys Tyr Arg Trp
725 730 735
Val Thr His Ala Gly Asn Lys Ser Ser Thr Glu Pro Met Pro Pro Arg
740 745 750
Gly Ser Leu Thr Gly Val Gln Thr Cys Arg Thr Ser Val
755 760 765

<210> 191
<211> 1329
<212> PRT
<213> Mus musculus

<400> 191
Met Pro Val Pro Pro Ala Arg Leu Leu Leu Leu Pro Leu Leu Pro Cys
1 5 10 15
Leu Leu Leu Leu Ala Pro Gly Thr Arg Gly Ala Pro Gly Cys Pro Val
20 25 30
Pro Ile Arg Gly Cys Lys Cys Ser Gly Glu Arg Pro Lys Gly Leu Ser
35 40 45
Gly Gly Ala His Asn Pro Ala Arg Arg Arg Val Val Cys Gly Gly Gly
50 55 60
Asp Leu Pro Glu Pro Pro Asp Pro Gly Leu Leu Pro Asn Gly Thr Ile
65 70 75 80
Thr Leu Leu Leu Ser Asn Asn Lys Ile Thr Gly Leu Arg Asn Gly Ser
85 90 95
Phe Leu Gly Leu Ser Leu Leu Glu Lys Leu Asp Leu Arg Ser Asn Val
100 105 110
Ile Ser Thr Val Gln Pro Gly Ala Phe Leu Gly Leu Gly Glu Leu Lys
115 120 125
Arg Leu Asp Leu Ser Asn Asn Arg Ile Gly Cys Leu Thr Ser Glu Thr
130 135 140
Phe Gln Gly Leu Pro Arg Leu Leu Arg Leu Asn Ile Ser Gly Asn Ile
145 150 155 160
Tyr Ser Ser Leu Gln Pro Gly Val Phe Asp Glu Leu Pro Ala Leu Lys
165 170 175
Ile Val Asp Phe Gly Thr Glu Phe Leu Thr Cys Asp Cys Arg Leu Arg
180 185 190
Trp Leu Leu Pro Trp Ala Arg Asn His Ser Leu Gln Leu Ser Glu Arg
195 200 205
Thr Leu Cys Ala Tyr Pro Ser Ala Leu His Ala His Ala Leu Ser Ser
210 215 220
Leu Gln Glu Ser Gln Leu Arg Cys Glu Gly Ala Leu Glu Leu His Thr
225 230 235 240
His Tyr Leu Ile Pro Ser Leu Arg Gln Val Val Phe Gln Gly Asp Arg
245 250 255
Leu Pro Phe Gln Cys Ser Ala Ser Tyr Leu Gly Asn Asp Thr Arg Ile
260 265 270
His Trp Tyr His Asn Gly Ala Pro Met Glu Ser Asp Glu Gln Ala Gly
275 280 285
Ile Val Leu Ala Glu Asn Leu Ile His Asp Cys Thr Phe Ile Thr Ser
290 295 300
Glu Leu Thr Leu Ser His Ile Gly Val Trp Ala Ser Gly Glu Trp Glu
305 310 315 320
Cys Ser Val Ser Thr Val Gln Gly Asn Thr Ser Lys Lys Val Glu Ile
325 330 335

Val Val Leu Glu Thr Ser Ala Ser Tyr Cys Pro Ala Glu Arg Val Thr
340 345 350
Asn Asn Arg Gly Asp Phe Arg Trp Pro Arg Thr Leu Ala Gly Ile Thr
355 360 365
Ala Tyr Gln Ser Cys Leu Gln Tyr Pro Phe Thr Ser Val Pro Leu Ser
370 375 380
Gly Gly Ala Pro Gly Thr Arg Ala Ser Arg Arg Cys Asp Arg Ala Gly
385 390 395 400
Arg Trp Glu Pro Gly Asp Tyr Ser His Cys Leu Tyr Thr Asn Asp Ile
405 410 415
Thr Arg Val Leu Tyr Thr Phe Val Leu Met Pro Ile Asn Ala Ser Asn
420 425 430
Ala Leu Thr Leu Ala His Gln Leu Arg Val Tyr Thr Ala Glu Ala Ala
435 440 445
Ser Phe Ser Asp Met Met Asp Val Val Tyr Val Ala Gln Met Ile Gln
450 455 460
Lys Phe Leu Gly Tyr Val Asp Gln Ile Lys Glu Leu Val Glu Val Met
465 470 475 480
Val Asp Met Ala Ser Asn Leu Met Leu Val Asp Glu His Leu Leu Trp
485 490 495
Leu Ala Gln Arg Glu Asp Lys Ala Cys Ser Gly Ile Val Gly Ala Leu
500 505 510
Glu Arg Ile Gly Gly Ala Ala Leu Ser Pro His Ala Gln His Ile Ser
515 520 525
Val Asn Ser Arg Asn Val Ala Leu Glu Ala Tyr Leu Ile Lys Pro His
530 535 540
Ser Tyr Val Gly Leu Thr Cys Thr Ala Phe Gln Arg Arg Glu Val Gly
545 550 555 560
Val Ser Gly Ala Gln Pro Ser Ser Val Gly Gln Asp Ala Pro Val Glu
565 570 575
Pro Glu Pro Leu Ala Asp Gln Gln Leu Arg Phe Arg Cys Thr Thr Gly
580 585 590
Arg Pro Asn Ile Ser Leu Ser Ser Phe His Ile Lys Asn Ser Val Ala
595 600 605
Leu Ala Ser Ile Gln Leu Pro Pro Ser Leu Phe Ser Thr Leu Pro Ala
610 615 620
Ala Leu Ala Pro Pro Val Pro Pro Asp Cys Thr Leu Gln Leu Leu Val
625 630 635 640
Phe Arg Asn Gly Arg Leu Phe Arg Ser His Gly Asn Asn Thr Ser Arg
645 650 655
Pro Gly Ala Ala Gly Pro Gly Lys Arg Arg Gly Val Ala Thr Pro Val
660 665 670
Ile Phe Ala Gly Thr Ser Gly Cys Gly Val Gly Asn Leu Thr Glu Pro
675 680 685
Val Ala Val Ser Leu Arg His Trp Ala Glu Gly Ala Asp Pro Met Ala
690 695 700
Ala Trp Trp Asn Gln Asp Gly Pro Gly Gly Trp Ser Ser Glu Gly Cys
705 710 715 720
Arg Leu Arg Tyr Ser Gln Pro Asn Val Ser Ser Leu Tyr Cys Gln His
725 730 735
Leu Gly Asn Val Ala Val Leu Met Glu Leu Asn Ala Phe Pro Arg Glu
740 745 750
Ala Gly Gly Ser Gly Ala Gly Leu His Pro Val Val Tyr Pro Cys Thr
755 760 765
Ala Leu Leu Leu Leu Cys Leu Phe Ser Thr Ile Ile Thr Tyr Ile Leu
770 775 780
Asn His Ser Ser Ile His Val Ser Arg Lys Gly Trp His Met Leu Leu
785 790 795 800
Asn Leu Cys Phe His Met Ala Met Thr Ser Ala Val Phe Val Gly Gly
805 810 815
Val Thr Leu Thr Asn Tyr Gln Met Val Cys Gln Ala Val Gly Ile Thr

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            820                 825                 830
Leu His Tyr Ser Ser Leu Ser Ser Leu Leu Trp Met Gly Val Lys Ala
        835                 840                 845
Arg Val Leu His Lys Glu Leu Ser Trp Arg Ala Pro Pro Leu Glu Glu
    850                 855                 860
Gly Glu Ala Ala Pro Pro Gly Pro Arg Pro Met Leu Arg Phe Tyr Leu
865                 870                 875                 880
Ile Ala Gly Gly Ile Pro Leu Ile Ile Cys Gly Ile Thr Ala Ala Val
                885                 890                 895
Asn Ile His Asn Tyr Arg Asp His Ser Pro Tyr Cys Trp Leu Val Trp
            900                 905                 910
Arg Pro Ser Leu Gly Ala Phe Tyr Ile Pro Val Ala Leu Ile Leu Pro
        915                 920                 925
Ile Thr Trp Ile Tyr Phe Leu Cys Ala Gly Leu His Leu Arg Ser His
    930                 935                 940
Val Ala Gln Asn Pro Lys Gln Gly Asn Arg Ile Ser Leu Glu Pro Gly
945                 950                 955                 960
Glu Glu Leu Arg Gly Ser Thr Arg Leu Arg Ser Ser Gly Val Leu Leu
                965                 970                 975
Asn Asp Ser Gly Ser Leu Leu Ala Thr Val Ser Ala Gly Val Gly Thr
            980                 985                 990
Pro Ala Pro Pro Glu Asp Gly Asp Gly Val Tyr Ser Pro Gly Val Gln
        995                 1000                1005
Leu Gly Ala Leu Met Thr Thr His Phe Leu Tyr Leu Ala Met Trp Ala
    1010                1015                1020
Cys Gly Ala Leu Ala Val Ser Gln Arg Trp Leu Pro Arg Val Val Cys
1025                1030                1035                1040
Ser Cys Leu Tyr Gly Val Ala Ala Ser Ala Leu Gly Leu Phe Val Phe
                1045                1050                1055
Thr His His Cys Ala Arg Arg Arg Asp Val Arg Ala Ser Trp Arg Ala
            1060                1065                1070
Cys Cys Pro Pro Ala Ser Pro Ser Ala Ser His Val Pro Ala Arg Ala
        1075                1080                1085
Leu Pro Thr Ala Thr Glu Asp Gly Ser Pro Val Leu Gly Glu Gly Pro
    1090                1095                1100
Ala Ser Leu Lys Ser Ser Pro Ser Gly Ser Ser Gly Arg Ala Pro Pro
1105                1110                1115                1120
Pro Pro Cys Lys Leu Thr Asn Leu Gln Val Ala Gln Ser Gln Val Cys
                1125                1130                1135
Glu Ala Ser Val Ala Ala Arg Gly Asp Gly Glu Pro Glu Pro Thr Gly
            1140                1145                1150
Ser Arg Gly Ser Leu Ala Pro Arg His His Asn Asn Leu His His Gly
        1155                1160                1165
Arg Arg Val His Lys Ser Arg Ala Lys Gly His Arg Ala Gly Glu Thr
    1170                1175                1180
Gly Gly Lys Ser Arg Leu Lys Ala Leu Arg Ala Gly Thr Ser Pro Gly
1185                1190                1195                1200
Ala Pro Glu Leu Leu Ser Ser Glu Ser Gly Ser Leu His Asn Ser Pro
                1205                1210                1215
Ser Asp Ser Tyr Pro Gly Ser Ser Arg Asn Ser Pro Gly Asp Gly Leu
            1220                1225                1230
Pro Leu Glu Gly Glu Pro Met Leu Thr Pro Ser Glu Gly Ser Asp Thr
        1235                1240                1245
Ser Ala Ala Pro Ile Ala Glu Thr Gly Arg Pro Gly Gln Arg Arg Ser
    1250                1255                1260
Ala Ser Arg Asp Asn Leu Lys Gly Ser Gly Ser Ala Leu Glu Arg Glu
1265                1270                1275                1280
Ser Lys Arg Arg Ser Tyr Pro Leu Asn Thr Thr Ser Leu Asn Gly Ala
                1285                1290                1295
Pro Lys Gly Gly Lys Tyr Glu Asp Ala Ser Val Thr Gly Ala Glu Ala
            1300                1305                1310
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Ile Ala Gly Gly Ser Met Lys Thr Gly Leu Trp Lys Ser Glu Thr Thr
1315 1320 1325
Val

<210> 192
<211> 500
<212> PRT
<213> Mus musculus

<400> 192
Met Arg Ala Gln Leu Trp Leu Leu Gln Leu Leu Leu Leu Arg Gly Ala
1 5 10 15
Ala Arg Ala Leu Ser Pro Ala Thr Pro Ala Gly His Asn Glu Gly Gln
20 25 30
Asp Ser Ala Trp Thr Ala Lys Arg Thr Arg Gln Gly Trp Ser Arg Arg
35 40 45
Pro Arg Glu Ser Pro Ala Gln Val Leu Lys Pro Gly Lys Thr Gln Leu
50 55 60
Ser Gln Asp Leu Gly Gly Gly Ser Leu Ala Ile Asp Thr Leu Pro Asp
65 70 75 80
Asn Arg Thr Arg Val Val Glu Asp Asn His Asn Tyr Tyr Val Ser Arg
85 90 95
Val Tyr Gly Pro Gly Glu Lys Gln Ser Gln Asp Leu Trp Val Asp Leu
100 105 110
Ala Val Ala Asn Arg Ser His Val Lys Ile His Arg Ile Leu Ser Ser
115 120 125
Ser His Arg Gln Ala Ser Arg Val Val Leu Ser Phe Asp Phe Pro Phe
130 135 140
Tyr Gly His Pro Leu Arg Gln Ile Thr Ile Ala Thr Gly Gly Phe Ile
145 150 155 160
Phe Met Gly Asp Met Leu His Arg Met Leu Thr Ala Thr Gln Tyr Val
165 170 175
Ala Pro Leu Met Ala Asn Phe Asn Pro Gly Tyr Ser Asp Asn Ser Thr
180 185 190
Val Ala Tyr Phe Asp Asn Gly Thr Val Phe Val Val Gln Trp Asp His
195 200 205
Val Tyr Leu Gln Asp Arg Glu Asp Arg Gly Ser Phe Thr Phe Gln Ala
210 215 220
Ala Leu His Arg Asp Gly Arg Ile Val Phe Gly Tyr Lys Glu Ile Pro
225 230 235 240
Met Ala Val Leu Asp Ile Ser Ser Ala Gln His Pro Val Lys Ala Gly
245 250 255
Leu Ser Asp Ala Phe Met Ile Leu Asn Ser Ser Pro Glu Val Pro Glu
260 265 270
Ser Gln Arg Arg Thr Ile Phe Glu Tyr His Arg Val Glu Leu Asp Ser
275 280 285
Ser Lys Ile Thr Thr Thr Ser Ala Val Glu Phe Thr Pro Leu Pro Thr
290 295 300
Cys Leu Gln His Gln Ser Cys Asp Thr Cys Val Ser Ser Asn Leu Thr
305 310 315 320
Phe Asn Cys Ser Trp Cys His Val Leu Gln Arg Cys Ser Ser Gly Phe
325 330 335
Asp Arg Tyr Arg Gln Glu Trp Leu Thr Tyr Gly Cys Ala Gln Glu Ala
340 345 350
Glu Gly Lys Thr Cys Glu Asp Phe Gln Asp Asp Ser His Tyr Ser Ala
355 360 365
Ser Pro Asp Ser Ser Phe Ser Pro Phe Asn Gly Asp Ser Thr Thr Ser
370 375 380
Ser Ser Leu Phe Ile Asp Ser Leu Thr Thr Glu Asp Asp Thr Lys Leu
385 390 395 400

Asn Pro Tyr Ala Glu Gly Asp Gly Leu Pro Asp His Ser Ser Pro Lys
405 410 415
Ser Lys Gly Pro Pro Val His Leu Gly Thr Ile Val Gly Ile Val Leu
420 425 430
Ala Val Leu Leu Val Ala Ala Ile Ile Leu Ala Gly Ile Tyr Ile Ser
435 440 445
Gly His Pro Asn Ser Asn Ala Ala Leu Phe Phe Ile Glu Arg Arg Pro
450 455 460
His His Trp Pro Ala Met Lys Phe His Asn His Pro Asn His Ser Thr
465 470 475 480
Tyr Thr Glu Val Glu Pro Ser Gly His Glu Lys Glu Gly Phe Val Glu
485 490 495
Ala Glu Gln Cys
500

<210> 193
<211> 530
<212> PRT
<213> Mus musculus

<400> 193
Met Ala Arg Phe Arg Arg Ala Asp Leu Ala Ala Ala Gly Val Met Leu
1 5 10 15
Leu Cys His Phe Leu Thr Asp Arg Phe His Phe Ala His Gly Glu Pro
20 25 30
Gly His His Thr Asn Asp Trp Ile Tyr Glu Val Thr Asn Ala Phe Pro
35 40 45
Trp Asn Glu Glu Gly Val Glu Val Asp Ser Gln Ala Tyr Asn His Arg
50 55 60
Trp Lys Arg Asn Val Asp Pro Phe Lys Ala Val Asp Thr Asn Arg Ala
65 70 75 80
Ser Met Gly Gln Ala Ser Pro Glu Ser Lys Gly Phe Thr Asp Leu Leu
85 90 95
Leu Asp Asp Gly Gln Asp Asn Asn Thr Gln Ile Glu Glu Asp Thr Asp
100 105 110
His Asn Tyr Tyr Ile Ser Arg Ile Tyr Gly Pro Ala Asp Ser Ala Ser
115 120 125
Arg Asp Leu Trp Val Asn Ile Asp Gln Met Glu Lys Asp Lys Val Lys
130 135 140
Ile His Gly Ile Leu Ser Asn Thr His Arg Gln Ala Ala Arg Val Asn
145 150 155 160
Leu Ser Phe Asp Phe Pro Phe Tyr Gly His Phe Leu Asn Glu Val Thr
165 170 175
Val Ala Thr Gly Gly Phe Ile Tyr Thr Gly Glu Val Val His Arg Met
180 185 190
Leu Thr Ala Thr Gln Tyr Ile Ala Pro Leu Met Ala Asn Phe Asp Pro
195 200 205
Ser Val Ser Arg Asn Ser Thr Val Arg Tyr Phe Asp Asn Gly Thr Ala
210 215 220
Leu Val Val Gln Trp Asp His Val His Leu Gln Asp Asn Tyr Asn Leu
225 230 235 240
Gly Ser Phe Thr Phe Gln Ala Thr Leu Leu Met Asp Gly Arg Ile Ile
245 250 255
Phe Gly Tyr Lys Glu Ile Pro Val Leu Val Thr Gln Ile Ser Ser Thr
260 265 270
Asn His Pro Val Lys Val Gly Leu Ser Asp Ala Phe Val Val Val His
275 280 285
Arg Ile Gln Gln Ile Pro Asn Val Arg Arg Arg Thr Ile Tyr Glu Tyr
290 295 300
His Arg Val Glu Leu Gln Met Ser Lys Ile Thr Asn Ile Ser Ala Val
305 310 315 320

```
Glu Met Thr Pro Leu Pro Thr Cys Leu Gln Phe Asn Gly Cys Gly Pro
                325                 330                 335
Cys Val Ser Ser Gln Ile Gly Phe Asn Cys Ser Trp Cys Ser Lys Leu
            340                 345                 350
Gln Arg Cys Ser Ser Gly Phe Asp Arg His Arg Gln Asp Trp Val Asp
        355                 360                 365
Ser Gly Cys Pro Glu Glu Val Gln Ser Lys Glu Lys Met Cys Glu Lys
    370                 375                 380
Thr Glu Pro Gly Glu Thr Ser Gln Thr Thr Thr Thr Ser His Thr Thr
385                 390                 395                 400
Thr Met Gln Phe Arg Val Leu Thr Thr Thr Arg Arg Ala Val Thr Ser
                405                 410                 415
Gln Met Pro Thr Ser Leu Pro Thr Glu Asp Asp Thr Lys Ile Ala Leu
            420                 425                 430
His Leu Lys Asp Ser Gly Ala Ser Thr Asp Asp Ser Ala Ala Glu Lys
        435                 440                 445
Lys Gly Gly Thr Leu His Ala Gly Leu Ile Val Gly Ile Leu Ile Leu
    450                 455                 460
Val Leu Ile Ile Ala Ala Ala Ile Leu Val Thr Val Tyr Met Tyr His
465                 470                 475                 480
His Pro Thr Ser Ala Ala Ser Ile Phe Phe Ile Glu Arg Arg Pro Ser
                485                 490                 495
Arg Trp Pro Ala Met Lys Phe Arg Arg Gly Ser Gly His Pro Ala Tyr
            500                 505                 510
Ala Glu Val Glu Pro Val Gly Glu Lys Glu Gly Phe Ile Val Ser Glu
        515                 520                 525
Gln Cys
    530

      <210> 194
      <211> 562
      <212> PRT
      <213> Mus musculus

      <400> 194
Met Asp Arg Ala Gly Arg Leu Gly Ala Gly Leu Arg Gly Leu Cys Val
 1               5                  10                  15
Ala Ala Leu Val Leu Val Cys Ala Gly His Gly Gly Arg Arg Glu Asp
            20                  25                  30
Gly Gly Pro Ala Cys Tyr Gly Gly Phe Asp Leu Tyr Phe Ile Leu Asp
        35                  40                  45
Lys Ser Gly Ser Val Leu His His Trp Asn Glu Ile Tyr Tyr Phe Val
    50                  55                  60
Glu Gln Leu Ala His Arg Phe Ile Ser Pro Gln Leu Arg Met Ser Phe
65                  70                  75                  80
Ile Val Phe Ser Thr Arg Gly Thr Thr Leu Met Lys Leu Thr Glu Asp
                85                  90                  95
Arg Glu Gln Ile Arg Gln Gly Leu Glu Glu Leu Gln Lys Val Leu Pro
            100                 105                 110
Gly Gly Asp Thr Tyr Met His Glu Gly Phe Glu Arg Ala Ser Glu Gln
        115                 120                 125
Ile Tyr Tyr Glu Asn Ser Gln Gly Tyr Arg Thr Ala Ser Val Ile Ile
    130                 135                 140
Ala Leu Thr Asp Gly Glu Leu His Glu Asp Leu Phe Phe Tyr Ser Glu
145                 150                 155                 160
Arg Glu Ala Asn Arg Ser Arg Asp Leu Gly Ala Ile Val Tyr Cys Val
                165                 170                 175
Gly Val Lys Asp Phe Asn Glu Thr Gln Leu Ala Arg Ile Ala Asp Ser
            180                 185                 190
Lys Asp His Val Phe Pro Val Asn Asp Gly Phe Gln Ala Leu Gln Gly
        195                 200                 205
```

Ile Ile His Ser Ile Leu Lys Lys Ser Cys Ile Glu Ile Leu Ala Ala
210 215 220
Glu Pro Ser Thr Ile Cys Ala Gly Glu Ser Phe Gln Val Val Val Arg
225 230 235 240
Gly Asn Gly Phe Arg His Ala Arg Asn Val Asp Arg Val Leu Cys Ser
245 250 255
Phe Lys Ile Asn Asp Ser Val Thr Leu Asn Glu Lys Pro Phe Ala Val
260 265 270
Glu Asp Thr Tyr Leu Leu Cys Pro Ala Pro Ile Leu Lys Glu Val Gly
275 280 285
Met Lys Ala Ala Leu Gln Val Ser Met Asn Asp Gly Leu Ser Phe Ile
290 295 300
Ser Ser Ser Val Ile Ile Thr Thr Thr His Cys Ser Asp Gly Ser Ile
305 310 315 320
Leu Ala Ile Ala Leu Leu Val Leu Phe Leu Leu Leu Ala Leu Ala Leu
325 330 335
Leu Trp Trp Phe Trp Pro Leu Cys Cys Thr Val Ile Ile Lys Glu Val
340 345 350
Pro Pro Pro Pro Val Glu Glu Ser Glu Glu Glu Asp Asp Asp Gly Leu
355 360 365
Pro Lys Lys Lys Trp Pro Thr Val Asp Ala Ser Tyr Tyr Gly Gly Arg
370 375 380
Gly Val Gly Gly Ile Lys Arg Met Glu Val Arg Trp Gly Glu Lys Gly
385 390 395 400
Ser Thr Glu Glu Gly Ala Lys Leu Glu Lys Ala Lys Asn Ala Arg Val
405 410 415
Lys Met Pro Glu Gln Glu Tyr Glu Phe Pro Glu Pro Arg Asn Leu Asn
420 425 430
Asn Asn Met Arg Arg Pro Ser Ser Pro Arg Lys Trp Tyr Ser Pro Ile
435 440 445
Lys Gly Lys Leu Asp Ala Leu Trp Val Leu Leu Arg Lys Gly Tyr Asp
450 455 460
Arg Val Ser Val Met Arg Pro Gln Pro Gly Asp Thr Gly Arg Cys Ile
465 470 475 480
Asn Phe Thr Arg Val Lys Asn Ser Gln Pro Ala Lys Tyr Pro Leu Asn
485 490 495
Asn Thr Tyr His Pro Ser Ser Pro Pro Pro Ala Pro Ile Tyr Thr Pro
500 505 510
Pro Pro Pro Ala Pro His Cys Pro Pro Pro Ala Pro Ser Ala Pro Thr
515 520 525
Pro Pro Ile Pro Ser Pro Pro Ser Thr Leu Pro Pro Pro Pro Gln Ala
530 535 540
Pro Pro Pro Asn Arg Ala Pro Pro Pro Ser Arg Pro Pro Pro Arg Pro
545 550 555 560
Ser Val

<210> 195
<211> 2565
<212> DNA
<213> Homo sapiens

<400> 195
tcgcgatgct gctgcgcctg ttgctggcct gggcggccgc agggcccaca ctgggccagg 60
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cacggcgccg caccttcctg gaggcctggc gggcctgccg cgagctgggg ggcgacctgg 180
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<212> PRT
<213> Homo sapiens

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35 40 45
Arg Ala Cys Arg Glu Leu Gly Gly Asp Leu Ala Thr Pro Arg Thr Pro
50 55 60
Glu Glu Ala Gln Arg Val Asp Ser Leu Val Gly Ala Gly Pro Ala Ser
65 70 75 80
Arg Leu Leu Trp Ile Gly Leu Gln Arg Gln Ala Arg Gln Cys Gln Leu
85 90 95
Gln Arg Pro Leu Arg Gly Phe Thr Trp Thr Thr Gly Asp Gln Asp Thr
100 105 110
Ala Phe Thr Asn Trp Ala Gln Pro Ala Ser Gly Gly Pro Cys Pro Ala
115 120 125
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130 135 140
Gly Ser Cys Thr Leu Ala Val Asp Gly Tyr Leu Cys Gln Phe Gly Phe

145 150 155 160
Glu Gly Ala Cys Pro Ala Leu Gln Asp Glu Ala Gly Gln Ala Gly Pro
165 170 175
Ala Val Tyr Thr Thr Pro Phe His Leu Val Ser Thr Glu Phe Glu Trp
180 185 190
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195 200 205
Ala Ser Leu Leu Cys Val Lys Gln Pro Glu Gly Gly Val Gly Trp Ser
210 215 220
Arg Ala Gly Pro Leu Cys Leu Gly Thr Gly Cys Ser Pro Asp Asn Gly
225 230 235 240
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245 250 255
Arg Cys Thr Glu Gly Phe Arg Leu Ala Ala Asp Gly Arg Ser Cys Glu
260 265 270
Asp Pro Cys Ala Gln Ala Pro Cys Glu Gln Gln Cys Glu Pro Gly Gly
275 280 285
Pro Gln Gly Tyr Ser Cys His Cys Arg Leu Gly Phe Arg Pro Ala Glu
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Asp Asp Pro His Arg Cys Val Asp Thr Asp Glu Cys Gln Ile Ala Gly
305 310 315 320
Val Cys Gln Gln Met Cys Val Asn Tyr Val Gly Gly Phe Glu Cys Tyr
325 330 335
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340 345 350
Ala Gly Ala Met Gly Ala Gln Ala Ser Gln Asp Leu Gly Asp Glu Leu
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370 375 380
Phe Asn Gly Gly Trp Thr Glu Met Pro Gly Ile Leu Trp Met Glu Pro
385 390 395 400
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405 410 415
Asp Arg Glu Pro Gln Ile Pro Tyr Pro Glu Pro Thr Trp Pro Pro Pro
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Arg Pro Val Val Val Ser Ala Thr His Pro Thr Leu Pro Ser Ala His
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Gln Pro Pro Val Ile Pro Ala Thr His Pro Ala Leu Ser Arg Asp His
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485 490 495
Gln Pro Gly Ile Leu Ser Val Ser His Ser Ala Gln Pro Pro Ala His
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Gln Pro Pro Met Ile Ser Thr Lys Tyr Pro Glu Leu Phe Pro Ala His
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Gln Ser Pro Met Phe Pro Asp Thr Arg Val Ala Gly Thr Gln Thr Thr
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Thr His Leu Pro Gly Ile Pro Pro Asn His Ala Pro Leu Val Thr Thr
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Leu Gly Ala Gln Leu Pro Pro Gln Ala Pro Asp Ala Leu Val Leu Arg
565 570 575
Thr Gln Ala Thr Gln Leu Pro Ile Ile Pro Thr Ala Gln Pro Ser Leu
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Thr Thr Thr Ser Arg Ser Pro Val Ser Pro Ala His Gln Ile Ser Val
595 600 605
Pro Ala Ala Thr Gln Pro Ala Ala Leu Pro Thr Leu Leu Pro Ser Gln
610 615 620
Ser Pro Thr Asn Gln Thr Ser Pro Ile Ser Pro Thr His Pro His Ser
625 630 635 640

Lys Ala Pro Gln Ile Pro Arg Glu Asp Gly Pro Ser Pro Lys Leu Ala
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Leu Trp Leu Pro Ser Pro Ala Pro Thr Ala Ala Pro Thr Ala Leu Gly
660 665 670
Glu Ala Gly Leu Ala Glu His Ser Gln Arg Asp Asp Arg Trp Leu Leu
675 680 685
Val Ala Leu Leu Val Pro Thr Cys Val Phe Leu Val Val Leu Leu Ala
690 695 700
Leu Gly Ile Val Tyr Cys Thr Arg Cys Gly Pro His Ala Pro Asn Lys
705 710 715 720
Arg Ile Thr Asp Cys Tyr Arg Trp Val Ile His Ala Gly Ser Lys Ser
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<211> 2973
<212> DNA
<213> Homo sapiens

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<211> 266
<212> PRT
<213> Homo sapiens

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35 40 45
Thr Pro Thr Ile Glu Asp Phe His Arg Lys Val Tyr Asn Ile Arg Gly
50 55 60
Asp Met Tyr Gln Leu Asp Ile Leu Asp Thr Ser Gly Asn His Pro Phe
65 70 75 80
Pro Ala Met Arg Arg Leu Ser Ile Leu Thr Gly Asp Val Phe Ile Leu
85 90 95
Val Phe Ser Leu Asp Asn Arg Glu Ser Phe Asp Glu Val Lys Arg Leu
100 105 110
Gln Lys Gln Ile Leu Glu Val Lys Ser Cys Leu Lys Asn Lys Thr Lys
115 120 125
Glu Ala Ala Glu Leu Pro Met Val Ile Cys Gly Asn Lys Asn Asp His
130 135 140
Gly Glu Leu Cys Arg Gln Val Pro Thr Thr Glu Ala Glu Leu Leu Val
145 150 155 160
Ser Gly Asp Glu Asn Cys Ala Tyr Phe Glu Val Ser Ala Lys Lys Asn
165 170 175
Thr Asn Val Asp Glu Met Phe Tyr Val Leu Phe Ser Met Ala Lys Leu
180 185 190
Pro His Glu Met Ser Pro Ala Leu His Arg Lys Ile Ser Val Gln Tyr
195 200 205
Gly Asp Ala Phe His Pro Arg Pro Phe Cys Met Arg Arg Val Lys Glu
210 215 220
Met Asp Ala Tyr Gly Met Val Ser Pro Phe Ala Arg Arg Pro Ser Val
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Ala Arg Glu Arg Asp Lys Cys Thr Ile Gln
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<210> 199
<211> 2159
<212> DNA
<213> Homo sapiens

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<210> 200
<211> 529
<212> PRT
<213> Homo sapiens

<400> 200

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His Thr Glu Glu Glu Val Glu Val Asp Ser His Ala Tyr Ser His Arg
    50                  55                  60
Trp Lys Arg Asn Leu Asp Phe Leu Lys Ala Val Asp Thr Asn Arg Ala
65                  70                  75                  80
Ser Val Gly Gln Asp Ser Pro Glu Pro Arg Ser Phe Thr Asp Leu Leu
                85                  90                  95
Leu Asp Asp Gly Gln Asp Asn Asn Thr Gln Ile Glu Glu Asp Thr Asp
            100                 105                 110
His Asn Tyr Tyr Ile Ser Arg Ile Tyr Gly Pro Ser Asp Ser Ala Ser
        115                 120                 125
Arg Asp Leu Trp Val Asn Ile Asp Gln Met Glu Lys Asp Lys Val Lys
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Ile His Gly Ile Leu Ser Asn Thr His Arg Gln Ala Ala Arg Val Asn
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225                 230                 235                 240
Gly Ser Phe Thr Phe Gln Ala Thr Leu Leu Met Asp Gly Arg Ile Ile
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Phe Gly Tyr Lys Glu Ile Pro Val Leu Val Thr Gln Ile Ser Ser Thr
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    290                 295                 300
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Glu Met Thr Pro Leu Pro Thr Cys Leu Gln Phe Asn Arg Cys Gly Pro
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Cys Val Ser Ser Gln Ile Gly Phe Asn Cys Ser Trp Cys Ser Lys Leu
            340                 345                 350
Gln Arg Cys Ser Ser Gly Phe Asp Arg His Arg Gln Asp Trp Val Asp
        355                 360                 365
Ser Gly Cys Pro Glu Glu Ser Lys Glu Lys Met Cys Glu Asn Thr Glu
    370                 375                 380
Pro Val Glu Thr Ser Ser Arg Thr Thr Thr Thr Ile Gly Ala Thr Thr
385                 390                 395                 400
Thr Gln Phe Arg Val Leu Thr Thr Thr Arg Arg Ala Val Thr Ser Gln
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Phe Pro Thr Ser Leu Pro Thr Glu Asp Asp Thr Lys Ile Ala Leu His
            420                 425                 430
Leu Lys Asp Asn Gly Ala Ser Thr Asp Asp Ser Ala Ala Glu Lys Lys
        435                 440                 445
Gly Gly Thr Leu His Ala Gly Leu Ile Val Gly Ile Leu Ile Leu Val
    450                 455                 460
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465                 470                 475                 480
Pro Thr Ser Ala Ala Ser Ile Phe Phe Ile Glu Arg Arg Pro Ser Arg
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Trp Pro Ala Met Lys Phe Arg Arg Gly Ser Gly His Pro Ala Tyr Ala
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<211> 2608
<212> DNA
<213> Homo sapiens

<400> 201

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<212> PRT
<213> Homo sapiens

<400> 204

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1090 1095 1100
Cys Asp Pro Ser Leu Val Asp Glu Ile Phe Asp Gln Ile Pro Glu Leu
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Leu Glu His His Glu Gln Phe Leu Glu Gln Val Arg His Cys Met Gln
1125 1130 1135
Thr Trp His Ala Gln Gln Lys Val Gly Ala Leu Leu Val Gln Ser Phe
1140 1145 1150
Ser Lys Asp Val Leu Val Asn Ile Tyr Ser Ala Tyr Ile Asp Asn Phe
1155 1160 1165
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1170 1175 1180
Phe Leu Lys Phe Leu Glu Gln Ser Met Arg Glu Asn Lys Glu Lys Gln
1185 1190 1195 1200
Ala Leu Ser Asp Leu Met Ile Lys Pro Val Gln Arg Ile Pro Arg Tyr
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Glu Leu Leu Val Lys Asp Leu Leu Lys His Thr Pro Glu Asp His Pro
1220 1225 1230
Asp His Pro Leu Leu Leu Glu Ala Gln Arg Asn Ile Lys Gln Val Ala
1235 1240 1245
Glu Arg Ile Asn Lys Gly Val Arg Ser Ala Glu Glu Ala Glu Arg His
1250 1255 1260
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1265 1270 1275 1280
Leu Gln Ala Pro Leu Arg Arg Phe Leu Arg Gln Glu Met Val Ile Glu
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Val Lys Ala Ile Gly Gly Lys Lys Asp Arg Ser Leu Phe Leu Phe Thr
1300 1305 1310
Asp Leu Ile Val Cys Thr Thr Leu Lys Arg Lys Ser Gly Ser Leu Arg
1315 1320 1325
Arg Ser Ser Met Ser Leu Tyr Thr Ala Ala Ser Val Ile Asp Thr Ala
1330 1335 1340
Ser Lys Tyr Lys Met Leu Trp Lys Leu Pro Leu Glu Asp Ala Asp Ile
1345 1350 1355 1360
Ile Lys Gly Ala Ser Gln Ala Thr Asn Arg Glu Asn Ile Gln Lys Ala
1365 1370 1375
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1380 1385 1390
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1395 1400 1405
Arg Asp Leu Ser Ala Ala Met His Arg Asp Leu Ser Glu Lys Gln Ala
1410 1415 1420
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1425 1430 1435 1440
Thr Arg Pro Glu Gly Thr Asp Ser Tyr Ile Phe Glu Phe Pro His Pro
1445 1450 1455
Asp Ala Arg Leu Gly Phe Glu Gln Ala Phe Asp Glu Ala Lys Arg Lys
1460 1465 1470
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1475 1480 1485
Pro Ile Met Lys Thr Arg Ser Gly Met Gln Phe Ser Cys Ala Ala Pro
1490 1495 1500
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Pro Asp Val Glu Ala Cys Ile Ala Val Cys Ser Ala Arg Ile Leu Cys
1540 1545 1550
Ile Gly Ala Val Pro Gly Leu Gln Pro Arg Cys His Arg Glu Pro Pro

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1570 1575 1580
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1585 1590 1595 1600
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1635 1640 1645
Gly Thr Leu Gln Ser Gln Ala Ser Arg Ser Thr Ile Ser Ser Ser Phe
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Gly Asn Glu Glu Thr Pro Ser Ser Lys Glu Ala Thr Ala Glu Thr Thr
1665 1670 1675 1680
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1730 1735 1740
Thr Glu Asp Gly Cys Val His Val Tyr Gln Ser Ser Asp Ser Ile Arg
1745 1750 1755 1760
Asp Arg Arg Asn Ser Met Lys Leu Gln His Ala Ala Ser Val Thr Cys
1765 1770 1775
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Val Ser Val Gly Gly Arg Leu Trp Cys Gly Cys Gln Asn Arg Val Leu
1825 1830 1835 1840
Val Leu Ser Pro Asp Thr Leu Gln Leu Glu His Met Phe Tyr Val Gly
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Gln Asp Ser Ser Arg Cys Val Ala Cys Met Val Asp Ser Ser Leu Gly
1860 1865 1870
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Asp Thr Phe Glu Gln Leu Ala Glu Val Asp Val Thr Pro Pro Val His
1890 1895 1900
Arg Met Leu Ala Gly Ser Asp Ala Ile Ile Arg Gln His Lys Ala Ala
1905 1910 1915 1920
Cys Leu Arg Ile Thr Ala Leu Leu Val Cys Glu Glu Leu Leu Trp Val
1925 1930 1935
Gly Thr Ser Ala Gly Val Val Leu Thr Met Pro Thr Ser Pro Gly Thr
1940 1945 1950
Val Ser Cys Pro Arg Ala Pro Leu Ser Pro Thr Gly Leu Gly Gln Gly
1955 1960 1965
His Thr Gly His Val Arg Phe Leu Ala Ala Val Gln Leu Pro Asp Gly
1970 1975 1980
Phe Asn Leu Leu Cys Pro Thr Pro Pro Pro Pro Pro Asp Thr Gly Pro
1985 1990 1995 2000
Glu Lys Leu Pro Ser Leu Glu His Arg Asp Ser Pro Trp His Arg Gly
2005 2010 2015
Pro Ala Pro Ala Arg Pro Lys Met Leu Val Ile Ser Gly Gly Asp Gly
2020 2025 2030
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<213> Homo sapiens

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<212> PRT
<213> Homo sapiens

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35 40 45
Gln Pro Trp His Ala Ala Leu Pro Ser Ser Pro Ala Pro Ala Pro Ala

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Arg Phe Val Leu Ser Gly Gly Arg Trp Glu Lys Thr Asp Leu Thr Tyr
            100                 105                 110
Arg Ile Leu Arg Phe Pro Trp Gln Leu Val Gln Glu Gln Val Arg Gln
        115                 120                 125
Thr Met Ala Glu Ala Leu Lys Val Trp Ser Asp Val Thr Pro Leu Thr
    130                 135                 140
Phe Thr Glu Val His Glu Gly Arg Ala Asp Ile Met Ile Asp Phe Ala
145                 150                 155                 160
Arg Tyr Trp His Gly Asp Asp Leu Pro Phe Asp Gly Pro Gly Gly Ile
                165                 170                 175
Leu Ala His Ala Phe Phe Pro Lys Thr His Arg Glu Gly Asp Val His
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Phe Asp Tyr Asp Glu Thr Trp Thr Ile Gly Asp Asp Gln Gly Thr Asp
        195                 200                 205
Leu Leu Gln Val Ala Ala His Glu Phe Gly His Val Leu Gly Leu Gln
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His Thr Thr Ala Ala Lys Ala Leu Met Ser Ala Phe Tyr Thr Phe Arg
225                 230                 235                 240
Tyr Pro Leu Ser Leu Ser Pro Asp Asp Cys Arg Gly Val Gln His Leu
                245                 250                 255
Tyr Gly Gln Pro Trp Pro Thr Val Thr Ser Arg Thr Pro Ala Leu Gly
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Pro Gln Ala Gly Ile Asp Thr Asn Glu Ile Ala Pro Leu Glu Pro Asp
        275                 280                 285
Ala Pro Pro Asp Ala Cys Glu Ala Ser Phe Asp Ala Val Ser Thr Ile
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Arg Gly Glu Leu Phe Phe Phe Lys Ala Gly Phe Val Trp Arg Leu Arg
305                 310                 315                 320
Gly Gly Gln Leu Gln Pro Gly Tyr Pro Ala Leu Ala Ser Arg His Trp
                325                 330                 335
Gln Gly Leu Pro Ser Pro Val Asp Ala Ala Phe Glu Asp Ala Gln Gly
            340                 345                 350
His Ile Trp Phe Phe Gln Gly Ala Gln Tyr Trp Val Tyr Asp Gly Glu
        355                 360                 365
Lys Pro Val Leu Gly Pro Ala Pro Leu Thr Glu Leu Gly Leu Val Arg
    370                 375                 380
Phe Pro Val His Ala Ala Leu Val Trp Gly Pro Glu Lys Asn Lys Ile
385                 390                 395                 400
Tyr Phe Phe Arg Gly Arg Asp Tyr Trp Arg Phe His Pro Ser Thr Arg
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Arg Val Asp Ser Pro Val Pro Arg Arg Ala Thr Asp Trp Arg Gly Val
            420                 425                 430
Pro Ser Glu Ile Asp Ala Ala Phe Gln Asp Ala Asp Gly Tyr Ala Tyr
        435                 440                 445
Phe Leu Arg Gly Arg Leu Tyr Trp Lys Phe Asp Pro Val Lys Val Lys
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35 40 45
Leu Ala Val Gln Tyr Leu Asn Thr Phe Tyr Gly Cys Pro Lys Glu Ser
50 55 60
Cys Asn Leu Phe Val Leu Lys Asp Thr Leu Lys Lys Met Gln Lys Phe
65 70 75 80
Phe Gly Leu Pro Gln Thr Gly Asp Leu Asp Gln Asn Thr Ile Glu Thr
85 90 95
Met Arg Lys Pro Arg Cys Gly Asn Pro Asp Val Ala Asn Tyr Asn Phe
100 105 110
Phe Pro Arg Lys Pro Lys Trp Asp Lys Asn Gln Ile Thr Tyr Arg Ile
115 120 125
Ile Gly Tyr Thr Pro Asp Leu Asp Pro Glu Thr Val Asp Asp Ala Phe
130 135 140
Ala Arg Ala Phe Gln Val Trp Ser Asp Val Thr Pro Leu Arg Phe Ser
145 150 155 160
Arg Ile His Asp Gly Glu Ala Asp Ile Met Ile Asn Phe Gly Arg Trp
165 170 175
Glu His Gly Asp Gly Tyr Pro Phe Asp Gly Lys Asp Gly Leu Leu Ala
180 185 190
His Ala Phe Ala Pro Gly Thr Gly Val Gly Gly Asp Ser His Phe Asp
195 200 205
Asp Asp Glu Leu Trp Thr Leu Gly Glu Gly Gln Val Val Arg Val Lys
210 215 220
Tyr Gly Asn Ala Asp Gly Glu Tyr Cys Lys Phe Pro Phe Leu Phe Asn
225 230 235 240
Gly Lys Glu Tyr Asn Ser Cys Thr Asp Thr Gly Arg Ser Asp Gly Phe
245 250 255
Leu Trp Cys Ser Thr Thr Tyr Asn Phe Glu Lys Asp Gly Lys Tyr Gly
260 265 270
Phe Cys Pro His Glu Ala Leu Phe Thr Met Gly Gly Asn Ala Glu Gly
275 280 285
Gln Pro Cys Lys Phe Pro Phe Arg Phe Gln Gly Thr Ser Tyr Asp Ser
290 295 300
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305 310 315 320
Glu Asp Tyr Asp Arg Asp Lys Lys Tyr Gly Phe Cys Pro Glu Thr Ala
325 330 335
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340 345 350
Phe Thr Phe Leu Gly Asn Lys Tyr Glu Ser Cys Thr Ser Ala Gly Arg
355 360 365
Ser Asp Gly Lys Met Trp Cys Ala Thr Thr Ala Asn Tyr Asp Asp Asp
370 375 380
Arg Lys Trp Gly Phe Cys Pro Asp Gln Gly Tyr Ser Leu Phe Leu Val
385 390 395 400
Ala Ala His Glu Phe Gly His Ala Met Gly Leu Glu His Ser Gln Asp
405 410 415
Pro Gly Ala Leu Met Ala Pro Ile Tyr Thr Tyr Thr Lys Asn Phe Arg
420 425 430
Leu Ser Gln Asp Asp Ile Lys Gly Ile Gln Glu Leu Tyr Gly Ala Ser
435 440 445
Pro Asp Ile Asp Leu Gly Thr Gly Pro Thr Pro Thr Leu Gly Pro Val
450 455 460
Thr Pro Glu Ile Cys Lys Gln Asp Ile Val Phe Asp Gly Ile Ala Gln
465 470 475 480
Ile Arg Gly Glu Ile Phe Phe Phe Lys Asp Arg Phe Ile Trp Arg Thr
485 490 495

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Trp Pro Glu Leu Pro Glu Lys Ile Asp Ala Val Tyr Glu Ala Pro Gln
        515                 520                 525
Glu Glu Lys Ala Val Phe Phe Ala Gly Asn Glu Tyr Trp Ile Tyr Ser
    530                 535                 540
Ala Ser Thr Leu Glu Arg Gly Tyr Pro Lys Pro Leu Thr Ser Leu Gly
545                 550                 555                 560
Leu Pro Pro Asp Val Gln Arg Val Asp Ala Ala Phe Asn Trp Ser Lys
                565                 570                 575
Asn Lys Lys Thr Tyr Ile Phe Ala Gly Asp Lys Phe Trp Arg Tyr Asn
            580                 585                 590
Glu Val Lys Lys Lys Met Asp Pro Gly Phe Pro Lys Leu Ile Ala Asp
        595                 600                 605
Ala Trp Asn Ala Ile Pro Asp Asn Leu Asp Ala Val Val Asp Leu Gln
    610                 615                 620
Gly Gly Gly His Ser Tyr Phe Phe Lys Gly Ala Tyr Tyr Leu Lys Leu
625                 630                 635                 640
Glu Asn Gln Ser Leu Lys Ser Val Lys Phe Gly Ser Ile Lys Ser Asp
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Trp Leu Gly Cys
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<213> Homo sapiens

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Gly Ile Ile Glu Lys Arg Arg Arg Asp Arg Ile Asn Ser Ser Leu Ser
50 55 60
Glu Leu Arg Arg Leu Val Pro Thr Ala Phe Glu Lys Gln Gly Ser Ser
65 70 75 80
Lys Leu Glu Lys Ala Glu Val Leu Gln Met Thr Val Asp His Leu Lys
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Met Leu His Ala Thr Gly Gly Thr Gly Phe Phe Asp Ala Arg Ala Leu
100 105 110
Ala Val Asp Phe Arg Ser Ile Gly Phe Arg Glu Cys Leu Thr Glu Val
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Glu Pro Ser Pro Thr Pro Thr Gly Pro Leu Ala Phe Pro Ala Trp Pro
                165                 170                 175
Trp Ser Phe Phe His Ser Cys Pro Gly Leu Pro Ala Leu Ser Asn Gln
            180                 185                 190
Leu Ala Ile Leu Gly Arg Val Pro Ser Pro Val Leu Pro Gly Val Ser
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Ser Pro Ala Tyr Pro Ile Pro Ala Leu Arg Thr Ala Pro Leu Arg Arg
    210                 215                 220
Ala Thr Gly Ile Ile Leu Pro Ala Arg Arg Asn Val Leu Pro Ser Arg
225                 230                 235                 240
Gly Ala Ser Ser Thr Arg Arg Ala Arg Pro Leu Glu Arg Pro Ala Thr
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Pro Val Pro Val Ala Pro Ser Ser Arg Ala Ala Arg Ser Ser His Ile
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Ala Pro Leu Leu Gln Ser Ser Ser Pro Thr Pro Pro Gly Pro Thr Gly
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Ser Ala Ala Tyr Val Ala Val Pro Thr Pro Asn Ser Ser Ser Pro Gly
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<212> PRT
<213> Homo sapiens

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Ser Ile Arg Ser Cys Lys Cys Ser Gly Glu Arg Pro Lys Gly Leu Ser
        35                  40                  45
Gly Gly Val Pro Gly Pro Ala Arg Arg Arg Val Val Cys Ser Gly Gly
    50                  55                  60
Asp Leu Pro Glu Pro Pro Glu Pro Gly Leu Leu Pro Asn Gly Thr Val
65                  70                  75                  80
Thr Leu Leu Leu Ser Asn Asn Lys Ile Thr Gly Leu Arg Asn Gly Ser
                85                  90                  95
Phe Leu Gly Leu Ser Leu Leu Glu Lys Leu Asp Leu Arg Asn Asn Ile
            100                 105                 110
Ile Ser Thr Val Gln Pro Gly Ala Phe Leu Gly Leu Gly Glu Leu Lys
        115                 120                 125
Arg Leu Asp Leu Ser Asn Asn Arg Ile Gly Cys Leu Thr Ser Glu Thr
    130                 135                 140
Phe Gln Gly Leu Pro Arg Leu Leu Arg Leu Asn Ile Ser Gly Asn Ile
145                 150                 155                 160
Phe Ser Ser Leu Gln Pro Gly Val Phe Asp Glu Leu Pro Ala Leu Lys
                165                 170                 175
Val Val Asp Leu Gly Thr Glu Phe Leu Thr Cys Asp Cys His Leu Arg
            180                 185                 190
Trp Leu Leu Pro Trp Ala Gln Asn Arg Ser Leu Gln Leu Ser Glu His
        195                 200                 205
Thr Leu Cys Ala Tyr Pro Ser Ala Leu His Ala Gln Ala Leu Gly Ser
    210                 215                 220
Leu Gln Glu Ala Gln Leu Cys Cys Glu Gly Ala Leu Glu Leu His Thr
225                 230                 235                 240
His His Leu Ile Pro Ser Leu Arg Gln Val Val Phe Gln Gly Asp Arg
                245                 250                 255
Leu Pro Phe Gln Cys Ser Ala Ser Tyr Leu Gly Asn Asp Thr Arg Ile
            260                 265                 270
Arg Trp Tyr His Asn Arg Ala Pro Val Glu Gly Asp Glu Gln Ala Gly
        275                 280                 285
Ile Leu Leu Ala Glu Ser Leu Ile His Asp Cys Thr Phe Ile Thr Ser
    290                 295                 300
Glu Leu Thr Leu Ser His Ile Gly Val Trp Ala Ser Gly Glu Trp Glu
305                 310                 315                 320
Cys Thr Val Ser Met Ala Gln Gly Asn Ala Ser Lys Lys Val Glu Ile
                325                 330                 335
Val Val Leu Glu Thr Ser Ala Ser Tyr Cys Pro Ala Glu Arg Val Ala
            340                 345                 350
Asn Asn Arg Gly Asp Phe Arg Trp Pro Arg Thr Leu Ala Gly Ile Thr
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405 410 415
Thr Arg Val Leu Tyr Thr Phe Val Leu Met Pro Ile Asn Ala Ser Asn
420 425 430
Ala Leu Thr Leu Ala His Gln Leu Arg Val Tyr Thr Ala Glu Ala Ala
435 440 445
Ser Phe Ser Asp Met Met Asp Val Val Tyr Val Ala Gln Met Ile Gln
450 455 460
Lys Phe Leu Gly Tyr Val Asp Gln Ile Lys Glu Leu Val Glu Val Met
465 470 475 480
Val Asp Met Ala Ser Asn Leu Met Leu Val Asp Glu His Leu Leu Trp
485 490 495
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Glu Arg Ile Gly Gly Ala Ala Leu Ser Pro His Ala Gln His Ile Ser
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Val Asn Ala Arg Asn Val Ala Leu Glu Ala Tyr Leu Ile Lys Pro His
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Ser Tyr Val Gly Leu Thr Cys Thr Ala Phe Gln Arg Arg Glu Gly Gly
545 550 555 560
Val Pro Gly Thr Arg Pro Gly Ser Pro Gly Gln Asn Pro Pro Pro Glu
565 570 575
Pro Glu Pro Pro Ala Asp Gln Gln Leu Arg Phe Arg Cys Thr Thr Gly
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Arg Pro Asn Val Ser Leu Ser Ser Phe His Ile Lys Asn Ser Val Ala
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Tyr Asp Gly Lys Gly Val Gly Leu Gly Pro Gly Pro Met Gly Leu Met
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Lys Asn Gly Ala Ala Ala Asp Ile Ile Phe Leu Val Asp Ser Ser Trp
        35                  40                  45
Thr Ile Gly Glu Glu His Phe Gln Leu Val Arg Glu Phe Leu Tyr Asp
    50                  55                  60
Val Val Lys Ser Leu Ala Val Gly Glu Asn Asp Phe His Phe Ala Leu
65                  70                  75                  80
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Val Gln Phe Asn Gly Asn Pro His Thr Glu Phe Leu Leu Asn Thr Tyr
                85                  90                  95
Arg Thr Lys Gln Glu Val Leu Ser His Ile Ser Asn Met Ser Tyr Ile
            100                 105                 110
Gly Gly Thr Asn Gln Thr Gly Lys Gly Leu Glu Tyr Ile Met Gln Ser
        115                 120                 125
His Leu Thr Lys Ala Ala Gly Ser Arg Ala Gly Asp Gly Val Pro Gln
    130                 135                 140
Val Ile Val Val Leu Thr Asp Gly His Ser Lys Asp Gly Leu Ala Leu
145                 150                 155                 160
Pro Ser Ala Glu Leu Lys Ser Ala Asp Val Asn Val Phe Ala Ile Gly
                165                 170                 175
Val Glu Asp Ala Asp Glu Gly Ala Leu Lys Glu Ile Ala Ser Glu Pro
            180                 185                 190
Leu Asn Met His Met Phe Asn Leu Glu Asn Phe Thr Ser Leu His Asp
        195                 200                 205
Ile Val Gly Asn Leu Val Ser Cys Val His Ser Ser Val Ser Pro Glu
    210                 215                 220
Arg Ala Gly Asp Thr Glu Thr Leu Lys Asp Ile Thr Ala Gln Asp Ser
225                 230                 235                 240
Ala Asp Ile Ile Phe Leu Ile Asp Gly Ser Asn Asn Thr Gly Ser Val
                245                 250                 255
Asn Phe Ala Val Ile Leu Asp Phe Leu Val Asn Leu Leu Glu Lys Leu
            260                 265                 270
Pro Ile Gly Thr Gln Gln Ile Arg Val Gly Val Val Gln Phe Ser Asp
        275                 280                 285
Glu Pro Arg Thr Met Phe Ser Leu Asp Thr Tyr Ser Thr Lys Ala Gln
    290                 295                 300
Val Leu Gly Ala Val Lys Ala Leu Gly Phe Ala Gly Gly Glu Leu Ala
305                 310                 315                 320
Asn Ile Gly Leu Ala Leu Asp Phe Val Val Glu Asn His Phe Thr Arg
                325                 330                 335
Ala Gly Gly Ser Arg Val Glu Glu Gly Val Pro Gln Val Leu Val Leu
            340                 345                 350
Ile Ser Ala Gly Pro Ser Ser Asp Glu Ile Arg Tyr Gly Val Val Ala
        355                 360                 365
Leu Lys Gln Ala Ser Val Phe Ser Phe Gly Leu Gly Ala Gln Ala Ala
    370                 375                 380
Ser Arg Ala Glu Leu Gln His Ile Ala Thr Asp Asp Asn Leu Val Phe
385                 390                 395                 400
Thr Val Pro Glu Phe Arg Ser Phe Gly Asp Leu Gln Glu Lys Leu Leu
                405                 410                 415
Pro Tyr Ile Val Gly Val Ala Gln Arg His Ile Val Leu Lys Pro Pro
            420                 425                 430
Thr Ile Val Thr Gln Val Ile Glu Val Asn Lys Arg Asp Ile Val Phe
        435                 440                 445
Leu Val Asp Gly Ser Ser Ala Leu Gly Leu Ala Asn Phe Asn Ala Ile
    450                 455                 460
Arg Asp Phe Ile Ala Lys Val Ile Gln Arg Leu Glu Ile Gly Gln Asp
465                 470                 475                 480
Leu Ile Gln Val Ala Val Ala Gln Tyr Ala Asp Thr Val Arg Pro Glu
                485                 490                 495
Phe Tyr Phe Asn Thr His Pro Thr Lys Arg Glu Val Ile Thr Ala Val
            500                 505                 510
Arg Lys Met Lys Pro Leu Asp Gly Ser Ala Leu Tyr Thr Gly Ser Ala
        515                 520                 525
Leu Asp Phe Val Arg Asn Asn Leu Phe Thr Ser Ser Ala Gly Tyr Arg
    530                 535                 540
Ala Ala Glu Gly Ile Pro Lys Leu Leu Val Leu Ile Thr Gly Gly Lys
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Ser Leu Asp Glu Ile Ser Gln Pro Ala Gln Glu Leu Lys Arg Ser Ser
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Ile Met Ala Phe Ala Ile Gly Asn Lys Gly Ala Asp Gln Ala Glu Leu
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Glu Glu Ile Ala Phe Asp Ser Ser Leu Val Phe Ile Pro Ala Glu Phe
        595                 600                 605
Arg Ala Ala Pro Leu Gln Gly Met Leu Pro Gly Leu Leu Ala Pro Leu
    610                 615                 620
Arg Thr Leu Ser Gly Thr Pro Glu Val His Ser Asn Lys Arg Asp Ile
625                 630                 635                 640
Ile Phe Leu Leu Asp Gly Ser Ala Asn Val Gly Lys Thr Asn Phe Pro
                645                 650                 655
Tyr Val Arg Asp Phe Val Met Asn Leu Val Asn Ser Leu Asp Ile Gly
            660                 665                 670
Asn Asp Asn Ile Arg Val Gly Leu Val Gln Phe Ser Asp Thr Pro Val
        675                 680                 685
Thr Glu Phe Ser Leu Asn Thr Tyr Gln Thr Lys Ser Asp Ile Leu Gly
    690                 695                 700
His Leu Arg Gln Leu Gln Leu Gln Gly Gly Ser Gly Leu Asn Thr Gly
705                 710                 715                 720
Ser Ala Leu Ser Tyr Val Tyr Ala Asn His Phe Thr Glu Ala Gly Gly
                725                 730                 735
Ser Arg Ile Arg Glu His Val Pro Gln Leu Leu Leu Leu Leu Thr Ala
            740                 745                 750
Gly Gln Ser Glu Asp Ser Tyr Leu Gln Ala Ala Asn Ala Leu Thr Arg
        755                 760                 765
Ala Gly Ile Leu Thr Phe Cys Val Gly Ala Ser Gln Ala Asn Lys Ala
    770                 775                 780
Glu Leu Glu Gln Ile Ala Phe Asn Pro Ser Leu Val Tyr Leu Met Asp
785                 790                 795                 800
Asp Phe Ser Ser Leu Pro Ala Leu Pro Gln Gln Leu Ile Gln Pro Leu
                805                 810                 815
Thr Thr Tyr Val Ser Gly Gly Val Glu Glu Val Pro Leu Ala Gln Pro
            820                 825                 830
Glu Ser Lys Arg Asp Ile Leu Phe Leu Phe Asp Gly Ser Ala Asn Leu
        835                 840                 845
Val Gly Gln Phe Pro Val Val Arg Asp Phe Leu Tyr Lys Ile Ile Asp
    850                 855                 860
Glu Leu Asn Val Lys Pro Glu Gly Thr Arg Ile Ala Val Ala Gln Tyr
865                 870                 875                 880
Ser Asp Asp Val Lys Val Glu Ser Arg Phe Asp Glu His Gln Ser Lys
                885                 890                 895
Pro Glu Ile Leu Asn Leu Val Lys Arg Met Lys Ile Lys Thr Gly Lys
            900                 905                 910
Ala Leu Asn Leu Gly Tyr Ala Leu Asp Tyr Ala Gln Arg Tyr Ile Phe
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Val Lys Ser Ala Gly Ser Arg Ile Glu Asp Gly Val Leu Gln Phe Leu
    930                 935                 940
Val Leu Leu Val Ala Gly Arg Ser Ser Asp Arg Val Asp Gly Pro Ala
945                 950                 955                 960
Ser Asn Leu Lys Gln Ser Gly Val Val Pro Phe Ile Phe Gln Ala Lys
                965                 970                 975
Asn Ala Asp Pro Ala Glu Leu Glu Gln Ile Val Leu Ser Pro Ala Phe
            980                 985                 990
Ile Leu Ala Ala Glu Ser Leu Pro Lys Ile Gly Asp Leu His Pro Gln
        995                 1000                1005
Ile Val Asn Leu Leu Lys Ser Val His Asn Gly Ala Pro Ala Pro Val
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Ser Gly Glu Lys Asp Val Val Phe Leu Leu Asp Gly Ser Glu Gly Val
1025                1030                1035                1040
Arg Ser Gly Phe Pro Leu Leu Lys Glu Phe Val Gln Arg Val Val Glu
                1045                1050                1055
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Gln Asp Val Val Asn Ala Val Arg Gln Leu Thr Leu Leu Gly Gly Pro
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Thr Pro Asn Thr Gly Ala Ala Leu Glu Phe Val Leu Arg Asn Ile Leu
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1125 1130 1135
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1140 1145 1150
Val Val Val Lys Arg Gly Gly Ala Val Pro Ile Gly Ile Gly Ile Gly
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Gly Phe Asp Thr Thr Arg Val Ala Val Ile Gln Phe Ser Asp Asp Pro
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Lys Ala Glu Phe Leu Leu Asn Ala His Ser Ser Lys Asp Glu Val Gln
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Asp Phe Val Ser Arg Ile Val Arg Arg Leu Asn Ile Gly Pro Ser Lys
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Tyr Leu Lys Thr Tyr Arg Ser Gln Ala Pro Val Leu Asp Ala Ile Arg
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Thr Ile Thr Asn Asp Pro Arg Leu Val Phe Thr Val Arg Glu Phe Arg
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Pro Glu Lys Lys Lys Ala Asp Ile Val Phe Leu Leu Asp Gly Ser Ile
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Ile Val Asp Thr Val Tyr Glu Asp Gly Asp Ser Ile Gln Val Gly Leu
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Ser Thr Lys Arg Gln Ile Ile Asp Ala Ile Asn Lys Val Val Tyr Lys
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Asn His Phe Val Pro Glu Ala Gly Ser Arg Leu Asp Gln Arg Val Pro
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Gln Ile Ala Phe Val Ile Thr Gly Gly Lys Ser Val Glu Asp Ala Gln
1745 1750 1755 1760
Asp Val Ser Leu Ala Leu Thr Gln Arg Gly Val Lys Val Phe Ala Val
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Gly Val Arg Asn Ile Asp Ser Glu Glu Val Gly Lys Ile Ala Ser Asn
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Ser Ala Thr Ala Phe Arg Val Gly Asn Val Gln Glu Leu Ser Glu Leu
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Ser Glu Gln Val Leu Glu Thr Leu His Asp Ala Met His Glu Thr Leu
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Cys Pro Gly Val Thr Asp Ala Ala Lys Ala Cys Asn Leu Asp Val Ile
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Leu Gly Phe Asp Gly Ser Arg Asp Gln Asn Val Phe Val Ala Gln Lys
1845 1850 1855
Gly Phe Glu Ser Lys Val Asp Ala Ile Leu Asn Arg Ile Ser Gln Met
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His Arg Val Ser Cys Ser Gly Gly Arg Ser Pro Thr Val Arg Val Ser
1875 1880 1885
Val Val Ala Asn Thr Pro Ser Gly Pro Val Glu Ala Phe Asp Phe Asp
1890 1895 1900
Glu Tyr Gln Pro Glu Met Leu Glu Lys Phe Arg Asn Met Arg Ser Gln
1905 1910 1915 1920
His Pro Tyr Val Leu Thr Glu Asp Thr Leu Lys Val Tyr Leu Asn Lys
1925 1930 1935
Phe Arg Gln Ser Ser Pro Asp Ser Val Lys Val Val Ile His Phe Thr
1940 1945 1950
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1955 1960 1965
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1970 1975 1980
Val Val Asn Leu Glu Arg Leu Met His Leu Glu Phe Gly Arg Gly Phe
1985 1990 1995 2000
Met Tyr Asp Arg Pro Leu Arg Leu Asn Leu Leu Asp Leu Asp Tyr Glu
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2020 2025 2030

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Tyr Ile Ala Tyr Leu Val Arg Gln Leu Asp Met Ser Pro Asp Pro Lys
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Tyr Gly Ser Lys Glu Lys Leu Val Asp Phe Leu Ser Arg Gly Met Thr
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Glu Pro Pro Gly Pro Tyr Phe Tyr Asp Leu Thr Val Thr Ser Ala His
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Asp Gln Ser Leu Val Leu Lys Gln Asn Leu Thr Val Thr Asp Arg Val
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<212> PRT
<213> Homo sapiens

<400> 220

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            20                  25                  30
Ser Leu Arg Leu Asp Cys Arg His Glu Asn Thr Ser Ser Ser Pro Ile
        35                  40                  45
Gln Tyr Glu Phe Ser Leu Thr Arg Glu Thr Lys Lys His Val Leu Phe
    50                  55                  60
Gly Thr Val Gly Val Pro Glu His Thr Tyr Arg Ser Arg Thr Asn Phe
65                  70                  75                  80
Thr Ser Lys Tyr His Met Lys Val Leu Tyr Leu Ser Ala Phe Thr Ser
                85                  90                  95
Lys Asp Glu Gly Thr Tyr Thr Cys Ala Leu His His Ser Gly His Ser
            100                 105                 110
Pro Pro Ile Ser Ser Gln Asn Val Thr Val Leu Arg Asp Lys Leu Val
        115                 120                 125
Lys Cys Glu Gly Ile Ser Leu Leu Ala Gln Asn Thr Ser Trp Leu Leu
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145                 150                 155                 160
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aaacagtagc atcgcc 736

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<211> 594
<212> DNA
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<211> 141
<212> PRT
<213> Homo sapiens

<400> 223
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Gly Ala Leu Ala Ser Ser Ser Lys Glu Glu Asn Arg Ile Ile Pro Gly
20 25 30
Gly Ile Tyr Asp Ala Asp Leu Asn Asp Glu Trp Val Gln Arg Ala Leu
35 40 45
His Phe Ala Ile Ser Glu Tyr Asn Lys Ala Thr Glu Asp Glu Tyr Tyr
50 55 60
Arg Arg Pro Leu Gln Val Leu Arg Ala Arg Glu Gln Thr Phe Gly Gly
65 70 75 80
Val Asn Tyr Phe Phe Asp Val Glu Val Gly Arg Thr Ile Cys Thr Lys
85 90 95
Ser Gln Pro Asn Leu Asp Thr Cys Ala Phe His Glu Gln Pro Glu Leu
100 105 110
Gln Lys Lys Gln Leu Cys Ser Phe Glu Ile Tyr Glu Val Pro Trp Glu
115 120 125
Asp Arg Met Ser Leu Val Asn Ser Arg Cys Gln Glu Ala
130 135 140

<210> 224
<211> 141
<212> PRT
<213> Homo sapiens

<400> 224
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Gly Ile Tyr Asn Ala Asp Leu Asn Asp Glu Trp Val Gln Arg Ala Leu
35 40 45
His Phe Ala Ile Ser Glu Tyr Asn Lys Ala Thr Lys Asp Asp Tyr Tyr
50 55 60
Arg Arg Pro Leu Arg Val Leu Arg Ala Arg Gln Gln Thr Val Gly Gly

65 70 75 80
Val Asn Tyr Phe Phe Asp Val Glu Val Gly Arg Thr Ile Cys Thr Lys
85 90 95
Ser Gln Pro Asn Leu Asp Thr Cys Ala Phe His Glu Gln Pro Glu Leu
100 105 110
Gln Lys Lys Gln Leu Cys Ser Phe Glu Ile Tyr Glu Val Pro Trp Glu
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<211> 5460
<212> DNA
<213> Homo sapiens

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gctgttgaag gaggatgttc ccatcttggt cagtcctatg cggatagaga tgtctggaag 240
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<210> 226
<211> 1466
<212> PRT
<213> Homo sapiens

<400> 226
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Ser His Leu Gly Gln Ser Tyr Ala Asp Arg Asp Val Trp Lys Pro Glu

35 40 45
Pro Cys Gln Ile Cys Val Cys Asp Ser Gly Ser Val Leu Cys Asp Asp
50 55 60
Ile Ile Cys Asp Asp Gln Glu Leu Asp Cys Pro Asn Pro Glu Ile Pro
65 70 75 80
Phe Gly Glu Cys Cys Ala Val Cys Pro Gln Pro Pro Thr Ala Pro Thr
85 90 95
Arg Pro Pro Asn Gly Gln Gly Pro Gln Gly Pro Lys Gly Asp Pro Gly
100 105 110
Pro Pro Gly Ile Pro Gly Arg Asn Gly Asp Pro Gly Ile Pro Gly Gln
115 120 125
Pro Gly Ser Pro Gly Ser Pro Gly Pro Pro Gly Ile Cys Glu Ser Cys
130 135 140
Pro Thr Gly Pro Gln Asn Tyr Ser Pro Gln Tyr Asp Ser Tyr Asp Val
145 150 155 160
Lys Ser Gly Val Ala Val Gly Gly Leu Ala Gly Tyr Pro Gly Pro Ala
165 170 175
Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Thr Ser Gly His Pro Gly
180 185 190
Ser Pro Gly Ser Pro Gly Tyr Gln Gly Pro Pro Gly Glu Pro Gly Gln
195 200 205
Ala Gly Pro Ser Gly Pro Pro Gly Pro Pro Gly Ala Ile Gly Pro Ser
210 215 220
Gly Pro Ala Gly Lys Asp Gly Glu Ser Gly Arg Pro Gly Arg Pro Gly
225 230 235 240
Glu Arg Gly Leu Pro Gly Pro Pro Gly Ile Lys Gly Pro Ala Gly Ile
245 250 255
Pro Gly Phe Pro Gly Met Lys Gly His Arg Gly Phe Asp Gly Arg Asn
260 265 270
Gly Glu Lys Gly Glu Thr Gly Ala Pro Gly Leu Lys Gly Glu Asn Gly
275 280 285
Leu Pro Gly Glu Asn Gly Ala Pro Gly Pro Met Gly Pro Arg Gly Ala
290 295 300
Pro Gly Glu Arg Gly Arg Pro Gly Leu Pro Gly Ala Ala Gly Ala Arg
305 310 315 320
Gly Asn Asp Gly Ala Arg Gly Ser Asp Gly Gln Pro Gly Pro Pro Gly
325 330 335
Pro Pro Gly Thr Ala Gly Phe Pro Gly Ser Pro Gly Ala Lys Gly Glu
340 345 350
Val Gly Pro Ala Gly Ser Pro Gly Ser Asn Gly Ala Pro Gly Gln Arg
355 360 365
Gly Glu Pro Gly Pro Gln Gly His Ala Gly Ala Gln Gly Pro Pro Gly
370 375 380
Pro Pro Gly Ile Asn Gly Ser Pro Gly Gly Lys Gly Glu Met Gly Pro
385 390 395 400
Ala Gly Ile Pro Gly Ala Pro Gly Leu Met Gly Ala Arg Gly Pro Pro
405 410 415
Gly Pro Ala Gly Ala Asn Gly Ala Pro Gly Leu Arg Gly Gly Ala Gly
420 425 430
Glu Pro Gly Lys Asn Gly Ala Lys Gly Glu Pro Gly Pro Arg Gly Glu
435 440 445
Arg Gly Glu Ala Gly Ile Pro Gly Val Pro Gly Ala Lys Gly Glu Asp
450 455 460
Gly Lys Asp Gly Ser Pro Gly Glu Pro Gly Ala Asn Gly Leu Pro Gly
465 470 475 480
Ala Ala Gly Glu Arg Gly Ala Pro Gly Phe Arg Gly Pro Ala Gly Pro
485 490 495
Asn Gly Ile Pro Gly Glu Lys Gly Pro Ala Gly Glu Arg Gly Ala Pro
500 505 510
Gly Pro Ala Gly Pro Arg Gly Ala Ala Gly Glu Pro Gly Arg Asp Gly
515 520 525

Val Pro Gly Gly Pro Gly Met Arg Gly Met Pro Gly Ser Pro Gly Gly
530 535 540
Pro Gly Ser Asp Gly Lys Pro Gly Pro Pro Gly Ser Gln Gly Glu Ser
545 550 555 560
Gly Arg Pro Gly Pro Pro Gly Pro Ser Gly Pro Arg Gly Gln Pro Gly
565 570 575
Val Met Gly Phe Pro Gly Pro Lys Gly Asn Asp Gly Ala Pro Gly Lys
580 585 590
Asn Gly Glu Arg Gly Gly Pro Gly Gly Pro Gly Pro Gln Gly Pro Pro
595 600 605
Gly Lys Asn Gly Glu Thr Gly Pro Gln Gly Pro Pro Gly Pro Thr Gly
610 615 620
Pro Gly Gly Asp Lys Gly Asp Thr Gly Pro Pro Gly Pro Gln Gly Leu
625 630 635 640
Gln Gly Leu Pro Gly Thr Gly Gly Pro Pro Gly Glu Asn Gly Lys Pro
645 650 655
Gly Glu Pro Gly Pro Lys Gly Asp Ala Gly Ala Pro Gly Ala Pro Gly
660 665 670
Gly Lys Gly Asp Ala Gly Ala Pro Gly Glu Arg Gly Pro Pro Gly Leu
675 680 685
Ala Gly Ala Pro Gly Leu Arg Gly Gly Ala Gly Pro Pro Gly Pro Glu
690 695 700
Gly Gly Lys Gly Ala Ala Gly Pro Pro Gly Pro Pro Gly Ala Ala Gly
705 710 715 720
Thr Pro Gly Leu Gln Gly Met Pro Gly Glu Arg Gly Gly Leu Gly Ser
725 730 735
Pro Gly Pro Lys Gly Asp Lys Gly Glu Pro Gly Gly Pro Gly Ala Asp
740 745 750
Gly Val Pro Gly Lys Asp Gly Pro Arg Gly Pro Thr Gly Pro Ile Gly
755 760 765
Pro Pro Gly Pro Ala Gly Gln Pro Gly Asp Lys Gly Glu Gly Gly Ala
770 775 780
Pro Gly Leu Pro Gly Ile Ala Gly Pro Arg Gly Ser Pro Gly Glu Arg
785 790 795 800
Gly Glu Thr Gly Pro Pro Gly Pro Ala Gly Phe Pro Gly Ala Pro Gly
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835 840 845
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Pro Gly Pro Pro Gly Ser Asn Gly Asn Pro Gly Pro Pro Gly Pro Ser
885 890 895
Gly Ser Pro Gly Lys Asp Gly Pro Pro Gly Pro Ala Gly Asn Thr Gly
900 905 910
Ala Pro Gly Ser Pro Gly Val Ser Gly Pro Lys Gly Asp Ala Gly Gln
915 920 925
Pro Gly Glu Lys Gly Ser Pro Gly Ala Gln Gly Pro Pro Gly Ala Pro
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945 950 955 960
Pro Pro Gly Met Pro Gly Pro Arg Gly Ser Pro Gly Pro Gln Gly Val
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1125 1130 1135
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1155 1160 1165
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1170 1175 1180
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Ala Pro Tyr Tyr Gly Asp Glu Pro Met Asp Phe Lys Ile Asn Thr Asp
1220 1225 1230
Glu Ile Met Thr Ser Leu Lys Ser Val Asn Gly Gln Ile Glu Ser Leu
1235 1240 1245
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Gln Asp Leu Gly Gly Gly Thr Leu Ala Met Asp Thr Leu Pro Asp Asn
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Arg Thr Arg Val Val Glu Asp Asn His Ser Tyr Tyr Val Ser Arg Leu
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Tyr Gly Pro Ser Glu Pro His Ser Arg Glu Leu Trp Val Asp Val Ala
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Glu Ala Asn Arg Ser Gln Val Lys Ile His Thr Ile Leu Ser Asn Thr
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His Arg Gln Ala Ser Arg Val Val Leu Ser Phe Asp Phe Pro Phe Tyr
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Gly His Pro Leu Arg Gln Ile Thr Ile Ala Thr Gly Gly Phe Ile Phe
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Met Gly Asp Val Ile His Arg Met Leu Thr Ala Thr Gln Tyr Val Ala
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Pro Leu Met Ala Asn Phe Asn Pro Gly Tyr Ser Asp Asn Ser Thr Val
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Val Tyr Phe Asp Asn Gly Thr Val Phe Val Val Gln Trp Asp His Val
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Pro Ile Lys Gly Lys Leu Asp Ala Leu Trp Val Leu Leu Arg Lys Gly
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Cys Ile Asn Phe Thr Arg Val Lys Asn Asn Gln Pro Ala Lys Tyr Pro
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Leu Asn Asn Ala Tyr His Thr Ser Ser Pro Pro Pro Ala Pro Ile Tyr
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Tyr Asp Gly Lys Gly Val Gly Leu Gly Pro Gly Pro Met Gly Leu Met
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Pro Gln Gly Ala Arg Gly Phe Pro Gly Thr Pro Gly Leu Pro Gly Phe
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Lys Gly Ile Arg Gly His Asn Gly Leu Asp Gly Leu Lys Gly Gln Pro
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Gly Ala Pro Gly Val Lys Gly Glu Pro Gly Ala Pro Gly Glu Asn Gly
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Thr Pro Gly Gln Thr Gly Ala Arg Gly Leu Pro Gly Glu Arg Gly Arg
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Val Gly Ala Pro Gly Pro Ala Gly Ala Arg Gly Ser Asp Gly Ser Val
225 230 235 240
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Phe Pro Gly Ala Pro Gly Pro Lys Gly Glu Ile Gly Ala Val Gly Asn
260 265 270
Ala Gly Pro Ala Gly Pro Ala Gly Pro Arg Gly Glu Val Gly Leu Pro
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Gly Leu Ser Gly Pro Val Gly Pro Pro Gly Asn Pro Gly Ala Asn Gly
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Leu Thr Gly Ala Lys Gly Ala Ala Gly Leu Pro Gly Val Ala Gly Ala
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Pro Gly Leu Pro Gly Pro Arg Gly Ile Pro Gly Pro Val Gly Ala Ala
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Gly Ala Thr Gly Ala Arg Gly Leu Val Gly Glu Pro Gly Pro Ala Gly
340 345 350
Ser Lys Gly Glu Ser Gly Asn Lys Gly Glu Pro Gly Ser Ala Gly Pro
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Gln Gly Pro Pro Gly Pro Ser Gly Glu Glu Gly Lys Arg Gly Pro Asn
370 375 380
Gly Glu Ala Gly Ser Ala Gly Pro Pro Gly Pro Pro Gly Leu Arg Gly
385 390 395 400
Ser Pro Gly Ser Arg Gly Leu Pro Gly Ala Asp Gly Arg Ala Gly Val

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Gly Pro Asn Gly Asp Ala Gly Arg Pro Gly Glu Pro Gly Leu Met Gly
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465 470 475 480
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485 490 495
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Ala Gly Leu Ala Gly Ala Arg Gly Ala Pro Gly Pro Asp Gly Asn Asn
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Gly Glu Phe Gly Leu Pro Gly Pro Ala Gly Pro Arg Gly Glu Arg Gly
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Pro Pro Gly Glu Ser Gly Ala Ala Gly Pro Thr Gly Pro Ile Gly Ser
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Arg Gly Pro Ser Gly Pro Pro Gly Pro Asp Gly Asn Lys Gly Glu Pro
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225 230 235 240
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755 760 765
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770 775 780
Val Tyr Gly Phe Lys Leu Gln Ser Leu Asp Leu Leu Leu Asp Thr Lys
785 790 795 800

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<212> DNA
<213> Homo sapiens

<400> 237

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<212> PRT
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Ser Lys His Gly Gly Asn Tyr Leu Leu Phe Asn Leu Ser Glu Arg Arg
50 55 60
Pro Asp Ile Thr Lys Leu His Ala Lys Val Leu Glu Phe Gly Trp Pro
65 70 75 80
Asp Leu His Thr Pro Ala Leu Glu Lys Ile Cys Ser Ile Cys Lys Ala
85 90 95
Met Asp Thr Trp Leu Asn Ala Asp Pro His Asn Val Val Val Leu His
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Asn Lys Gly Asn Arg Gly Arg Ile Gly Val Val Ile Ala Ala Tyr Met
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His Tyr Ser Asn Ile Ser Ala Ser Ala Asp Gln Ala Leu Asp Arg Phe
130 135 140
Ala Met Lys Arg Phe Tyr Glu Asp Lys Ile Val Pro Ile Gly Gln Pro
145 150 155 160
Ser Gln Arg Arg Tyr Val His Tyr Phe Ser Gly Leu Leu Ser Gly Ser
165 170 175
Ile Lys Ile Asn Asn Lys Pro Leu Phe Leu His His Val Ile Met His
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Gly Ile Pro Asn Phe Glu Ser Lys Gly Gly Cys Arg Pro Phe Leu Arg
195 200 205
Ile Tyr Gln Ala Met Gln Pro Val Tyr Thr Ser Gly Ile Tyr Asn Ile
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Pro Gly Asp Ser Gln Thr Ser Val Cys Ile Thr Ile Glu Pro Gly Leu
225 230 235 240
Leu Leu Lys Gly Asp Ile Leu Leu Lys Cys Tyr His Lys Lys Phe Arg
245 250 255
Ser Pro Ala Arg Asp Val Ile Phe Arg Val Gln Phe His Thr Cys Ala
260 265 270
Ile His Asp Leu Gly Val Val Phe Gly Lys Glu Asp Leu Asp Asp Ala
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Phe Lys Asp Asp Arg Phe Pro Glu Tyr Gly Lys Val Glu Phe Val Phe
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Ser Tyr Gly Pro Glu Lys Ile Gln Gly Met Glu His Leu Glu Asn Gly
305 310 315 320
Pro Ser Val Ser Val Asp Tyr Asn Thr Ser Asp Pro Leu Ile Arg Trp
325 330 335

Asp Ser Tyr Asp Asn Phe Ser Gly His Arg Asp Asp Gly Met Glu Glu
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Val Val Gly His Thr Gln Gly Pro Leu Asp Gly Ser Leu Tyr Ala Lys
355 360 365
Val Lys Lys Lys Asp Ser Leu His Gly Ser Thr Gly Ala Val Asn Ala
370 375 380
Thr Arg Pro Thr Leu Ser Ala Thr Pro Asn His Val Glu His Thr Leu
385 390 395 400
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405 410 415
Lys Thr Asp Glu Pro Val Pro Gly Ala Ser Ser Ala Thr Ala Ala Leu
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Ser Pro Gln Glu Lys Arg Glu Leu Asp Arg Leu Leu Ser Gly Phe Gly
435 440 445
Leu Glu Arg Glu Lys Gln Gly Ala Met Tyr His Thr Gln His Leu Arg
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465 470 475 480
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485 490 495
Glu Thr Asp Ile Leu Asp Asp Glu Leu Pro Asn Gln Asp Gly His Ser
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Ala Gly Ser Met Gly Thr Leu Ser Ser Leu Asp Gly Val Thr Asn Thr
515 520 525
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Asp Lys Ser Tyr Pro Met Glu Pro Met Val Asn Gly Gly Gly Tyr Pro
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Tyr Glu Ser Ala Ser Arg Ala Gly Pro Ala His Ala Gly His Thr Ala
565 570 575
Pro Met Arg Pro Ser Tyr Ser Ala Gln Glu Gly Leu Ala Gly Tyr Gln
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755 760 765
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770 775 780
Glu Ser Val Pro Pro Gly Arg Ser Tyr Ser Pro Tyr Asp Tyr Gln Pro
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Cys Leu Ala Gly Pro Asn Gln Asp Phe His Ser Lys Ser Pro Ala Ser
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Ser Ser Leu Pro Ala Phe Leu Pro Thr Thr His Ser Pro Pro Gly Pro

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Pro Leu Asn Leu Glu Gly Leu Val Ala His Arg Val Ala Gly Val Gln
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Ala Arg Glu Lys Gln Pro Ala Glu Pro Pro Ala Pro Leu Arg Arg Arg
                885                 890                 895
Ala Ala Ser Asp Gly Gln Tyr Glu Asn Gln Ser Pro Glu Ala Thr Ser
            900                 905                 910
Pro Arg Ser Pro Gly Val Arg Ser Pro Val Gln Cys Val Ser Pro Glu
        915                 920                 925
Leu Ala Leu Thr Ile Ala Leu Asn Pro Gly Gly Arg Pro Lys Glu Pro
    930                 935                 940
His Leu His Ser Tyr Lys Glu Ala Phe Glu Glu Met Glu Gly Thr Ser
945                 950                 955                 960
Pro Ser Ser Pro Pro Pro Ser Gly Val Arg Ser Pro Pro Gly Leu Ala
                965                 970                 975
Lys Thr Pro Leu Ser Ala Leu Gly Leu Lys Pro His Asn Pro Ala Asp
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Ile Leu Leu His Pro Thr Gly Val Thr Arg Arg Arg Ile Gln Pro Glu
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Tyr Val Glu Ser Val Ala Arg Thr Ala Val Ala Gly Pro Arg Ala Gln
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Asp Ser Glu Pro Lys Ser Phe Ser Ala Pro Ala Thr Gln Ala Tyr Gly
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His Glu Ile Pro Leu Arg Asn Gly Thr Leu Gly Gly Ser Phe Val Ser
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Leu Pro Thr Val Gly Ser Ser Tyr Ser Ser Pro Asp Tyr Ser Leu Gln
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His Phe Ser Ser Ser Pro Glu Ser Gln Ala Arg Ala Gln Phe Ser Val
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Val Gly Thr Asn Thr Pro Pro Ser Pro Gly Phe Gly Arg Arg Ala Ile
1185                1190                1195                1200
Asn Pro Ser Met Ala Ala Pro Ser Ser Pro Ser Leu Ser His His Gln
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Met Met Gly Pro Pro Gly Thr Gly Phe His Gly Ser Thr Val Ser Ser
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Pro Gln Ser Ser Ala Ala Thr Thr Pro Gly Ser Pro Ser Leu Cys Arg
        1235                1240                1245
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Thr Thr Pro Gly Ser Pro Ser Leu Gly Arg His Pro Gly Ala His Gln
1265                1270                1275                1280
Gly Asn Leu Ala Ser Gly Leu His Ser Asn Ala Ile Ala Ser Pro Gly
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Ser Pro Ser Leu Gly Arg His Leu Gly Gly Ser Gly Ser Val Val Pro
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1345 1350 1355 1360
Pro Gly Leu Ser Ser Pro Ala Thr Ser Pro Ser Pro Asp Ser Ala Ala
1365 1370 1375
Phe Arg Gln Gly Ser Pro Thr Pro Ala Leu Pro Glu Lys Arg Arg Met
1380 1385 1390
Ser Val Gly Asp Arg Ala Gly Ser Leu Pro Asn Tyr Ala Thr Ile Asn
1395 1400 1405
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1410 1415 1420
Gly Ser Thr Val Ser Phe Ser His Thr Leu Pro Asp Phe Ser Lys Tyr
1425 1430 1435 1440
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1445 1450 1455
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1460 1465 1470
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1475 1480 1485
Asp Ser His Ser Phe Arg Gly Ala Tyr Gly Leu Ala Met Lys Val Ser
1490 1495 1500
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1585 1590 1595 1600
Val Leu Phe Ile Asn Ser Val Asp Met Glu Ser Leu Thr Gly Pro Gln
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1620 1625 1630
Ala Ala Thr Ile Val His Phe Lys Val Ser Ala Gln Gly Ile Thr Leu
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Thr Asp Asn Gln Arg Lys Leu Phe Phe Arg Arg His Tyr Pro Leu Asn
1650 1655 1660
Thr Val Thr Phe Cys Asp Leu Asp Pro Gln Glu Arg Lys Trp Met Lys
1665 1670 1675 1680
Thr Glu Gly Gly Ala Pro Ala Lys Leu Phe Gly Phe Val Ala Arg Lys
1685 1690 1695
Gln Gly Ser Thr Thr Cys His Leu Phe Ala Glu Leu Asp Pro Asn Gln
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Ala Ala Ala Phe Leu Gly Asp Ile Ala Leu Asp Glu Glu Asp Leu Arg
50 55 60
Ala Phe Gln Val Gln Gln Ala Val Asp Leu Arg Arg His Thr Ala Arg
65 70 75 80
Lys Ser Ser Ile Lys Ala Ala Val Pro Gly Asn Thr Ser Thr Pro Ser
85 90 95
Cys Gln Ser Thr Asn Gly Gln Pro Gln Arg Gly Ala Cys Gly Arg Trp
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Arg Gly Arg Ser Arg Ser Arg Arg Ala Ala Thr Ser Arg Pro Glu Arg
115 120 125
Val Trp Pro Asp Gly Val Ile Pro Phe Val Ile Gly Gly Asn Phe Thr
130 135 140
Gly Ser Gln Arg Ala Val Phe Arg Gln Ala Met Arg His Trp Glu Lys
145 150 155 160
His Thr Cys Val Thr Phe Leu Glu Arg Thr Asp Glu Asp Ser Tyr Ile
165 170 175
Val Phe Thr Tyr Arg Pro Cys Gly Cys Cys Ser Tyr Val Gly Arg Arg
180 185 190
Gly Gly Gly Pro Gln Ala Ile Ser Ile Gly Lys Asn Cys Asp Lys Phe
195 200 205
Gly Ile Val Val His Glu Leu Gly His Val Val Gly Phe Trp His Glu
210 215 220
His Thr Arg Pro Asp Arg Asp Arg His Val Ser Ile Val Arg Glu Asn
225 230 235 240
Ile Gln Pro Gly Gln Glu Tyr Asn Phe Leu Lys Met Glu Pro Gln Glu
245 250 255
Val Glu Ser Leu Gly Glu Thr Tyr Asp Phe Asp Ser Ile Met His Tyr
260 265 270
Ala Arg Asn Thr Phe Ser Arg Gly Ile Phe Leu Asp Thr Ile Val Pro
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Lys Tyr Glu Val Asn Gly Val Lys Pro Pro Ile Gly Gln Arg Thr Arg
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Ala Ile Cys Gly Gly Asp Val Lys Lys Asp Tyr Gly His Ile Gln Ser

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Asp Gly His Ser Glu Ser Ser Thr Leu Ile Gly Arg Tyr Cys Gly Tyr
            500                 505                 510
Glu Lys Pro Asp Asp Ile Lys Ser Thr Ser Ser Arg Leu Trp Leu Lys
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Phe Val Ser Asp Gly Ser Ile Asn Lys Ala Gly Phe Ala Val Asn Phe
    530                 535                 540
Phe Lys Glu Val Asp Glu Cys Ser Arg Pro Asn Arg Gly Gly Cys Glu
545                 550                 555                 560
Gln Arg Cys Leu Asn Thr Leu Gly Ser Tyr Lys Cys Ser Cys Asp Pro
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Gly Tyr Glu Leu Ala Pro Asp Lys Arg Arg Cys Glu Ala Ala Cys Gly
            580                 585                 590
Gly Phe Leu Thr Lys Leu Asn Gly Ser Ile Thr Ser Pro Gly Trp Pro
        595                 600                 605
Lys Glu Tyr Pro Pro Asn Lys Asn Cys Ile Trp Gln Leu Val Ala Pro
    610                 615                 620
Thr Gln Tyr Arg Ile Ser Leu Gln Phe Asp Phe Phe Glu Thr Glu Gly
625                 630                 635                 640
Asn Asp Val Cys Lys Tyr Asp Phe Val Glu Val Arg Ser Gly Leu Thr
                645                 650                 655
Ala Asp Ser Lys Leu His Gly Lys Phe Cys Gly Ser Glu Lys Pro Glu
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Val Ile Thr Ser Gln Tyr Asn Asn Met Arg Val Glu Phe Lys Ser Asp
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Asp Asn Lys His Asp Cys Lys Glu Ala Gly Cys Asp His Lys Val Thr
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Ser Thr Ser Gly Thr Ile Thr Ser Pro Asn Trp Pro Asp Lys Tyr Pro
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Val Lys Leu Thr Phe Met Glu Met Asp Ile Glu Ser Gln Pro Glu Cys
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Ala Tyr Asp His Leu Glu Val Phe Asp Gly Arg Asp Ala Lys Ala Pro
                805                 810                 815
Val Leu Gly Arg Phe Cys Gly Ser Lys Lys Pro Glu Pro Val Leu Ala
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Thr Gly Ser Arg Met Phe Leu Arg Phe Tyr Ser Asp Asn Ser Val Gln
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Glu Glu Thr Asp Cys Gly Tyr Asp Tyr Met Glu Leu Phe Asp Gly Tyr
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<212> PRT
<213> Homo sapiens

<400> 246

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        35                  40                  45
Lys Leu Thr Ala Cys Leu Gln Gly Gln Gln Gly Ala Glu Ala Asp Lys
    50                  55                  60
Arg Ser Lys Lys Leu Pro Leu Thr Thr Leu Ala Gln Cys Leu Met Glu
65                  70                  75                  80
Gly Ser Ala Ile Leu Gly Asp Asp Thr Leu Leu Gly Lys Met Leu Lys
                85                  90                  95
Leu Cys Gly Glu Thr Glu Asp Lys Leu Ala Gln Glu Leu Ile His Phe
            100                 105                 110
Glu Leu Gln Val Glu Arg Asp Val Ile Glu Pro Leu Phe Leu Leu Ala
        115                 120                 125
Glu Val Glu Ile Pro Asn Ile Gln Lys Gln Arg Lys His Leu Ala Lys
    130                 135                 140
Leu Val Leu Asp Met Asp Ser Ser Arg Thr Arg Trp Gln Gln Thr Ser
145                 150                 155                 160
Lys Ser Ser Gly Leu Ser Ser Ser Leu Gln Pro Ala Gly Ala Lys Ala
                165                 170                 175
Asp Ala Leu Arg Glu Glu Met Glu Glu Ala Ala Asn Arg Val Glu Ile
            180                 185                 190
Cys Arg Asp Gln Leu Ser Ala Asp Met Tyr Ser Phe Val Ala Lys Glu
        195                 200                 205
Ile Asp Tyr Ala Asn Tyr Phe Gln Thr Leu Ile Glu Val Gln Ala Glu
    210                 215                 220
Tyr His Arg Lys Ser Leu Thr Leu Leu Gln Ala Val Leu Pro Gln Ile
225                 230                 235                 240
Lys Ala Gln Gln Glu Ala Trp Val Glu Lys Pro Ser Phe Gly Lys Pro
                245                 250                 255
Leu Glu Glu His Leu Thr Ile Ser Gly Arg Glu Ile Ala Phe Pro Ile
            260                 265                 270
Glu Ala Cys Val Thr Met Leu Leu Glu Cys Gly Met Gln Glu Glu Gly
        275                 280                 285
Leu Phe Arg Val Ala Pro Ser Ala Ser Lys Leu Lys Lys Leu Lys Ala
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Ala Leu Asp Cys Cys Val Val Asp Val Gln Glu Tyr Ser Ala Asp Pro
305                 310                 315                 320
His Ala Ile Ala Gly Ala Leu Lys Ser Tyr Leu Arg Glu Leu Pro Glu
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Pro Leu Met Thr Phe Glu Leu Tyr Asp Glu Trp Ile Gln Ala Ser Asn
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Val Gln Glu Gln Asp Lys Lys Leu Gln Ala Leu Trp Asn Ala Cys Glu
355 360 365
Lys Leu Pro Lys Ala Asn His Asn Asn Ile Arg Tyr Leu Ile Lys Phe
370 375 380
Leu Ser Lys Leu Ser Glu Tyr Gln Asp Val Asn Lys Met Thr Pro Ser
385 390 395 400
Asn Met Ala Ile Val Leu Gly Pro Asn Leu Leu Trp Pro Gln Ala Glu
405 410 415
Gly Asn Ile Thr Glu Met Met Thr Thr Val Ser Leu Gln Ile Val Gly
420 425 430
Ile Ile Glu Pro Ile Ile Gln His Ala Asp Trp Phe Phe Pro Gly Glu
435 440 445
Ile Glu Phe Asn Ile Thr Gly Asn Tyr Gly Ser Pro Val His Val Asn
450 455 460
His Asn Ala Asn Tyr Ser Ser Met Pro Ser Pro Asp Met Asp Pro Ala
465 470 475 480
Asp Arg Arg Gln Pro Glu Gln Ala Arg Arg Pro Leu Ser Val Ala Thr
485 490 495
Asp Asn Met Met Leu Glu Phe Tyr Lys Lys Asp Gly Leu Arg Lys Ile
500 505 510
Gln Ser Met Gly Val Arg Val Met Asp Thr Asn Trp Val Ala Arg Arg
515 520 525
Gly Ser Ser Ala Gly Arg Lys Val Ser Cys Ala Pro Pro Ser Met Gln
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Pro Pro Ala Pro Pro Ala Glu Leu Ala Ala Pro Leu Pro Ser Pro Leu
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Pro Glu Gln Pro Leu Asp Ser Pro Ala Ala Pro Ala Leu Ser Pro Ser
565 570 575
Gly Leu Gly Leu Gln Pro Gly Pro Glu Arg Thr Ser Thr Thr Lys Ser
580 585 590
Lys Glu Leu Ser Pro Gly Ser Ala Gln Lys Gly Ser Pro Gly Ser Ser
595 600 605
Gln Gly Thr Ala Cys Ala Gly Thr Gln Pro Gly Ala Gln Pro Gly Ala
610 615 620
Gln Pro Gly Ala Ser Pro Ser Pro Ser Gln Pro Pro Ala Asp Gln Ser
625 630 635 640
Pro His Thr Leu Arg Lys Val Ser Lys Lys Leu Ala Pro Ile Pro Pro
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Lys Val Pro Phe Gly Gln Pro Gly Ala Met Ala Asp Gln Ser Ala Gly
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Gln Leu Ser Pro Val Ser Leu Ser Pro Thr Pro Pro Ser Thr Pro Ser
675 680 685
Pro Tyr Gly Leu Ser Tyr Pro Gln Gly Tyr Ser Leu Ala Ser Gly Gln
690 695 700
Leu Ser Pro Ala Ala Ala Pro Pro Leu Ala Ser Pro Ser Val Phe Thr
705 710 715 720
Ser Thr Leu Ser Lys Ser Arg Pro Thr Pro Lys Pro Arg Gln Arg Pro
725 730 735
Thr Leu Pro Pro Gln Pro Pro Thr Val Asn Leu Ser Ala Ser Ser
740 745 750
Pro Gln Ser Thr Glu Ala Pro Met Leu Asp Gly Met Ser Pro Gly Glu
755 760 765
Ser Met Ser Thr Asp Leu Val His Phe Asp Ile Pro Ser Ile His Ile
770 775 780
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785 790 795 800
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Ala Leu

<210> 247
<211> 2850
<212> DNA
<213> Homo sapiens

<400> 247
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<212> PRT
<213> Homo sapiens

<400> 248

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35 40 45
Cys Glu Val Thr Tyr Asp Lys Thr Pro Leu Glu Lys Asp Gly Ile Thr
50 55 60
Val Val Asp Trp Pro Phe Asp Asp Gly Ala Pro Pro Pro Gly Lys Val
65 70 75 80
Val Glu Asp Trp Leu Ser Leu Val Lys Ala Lys Phe Cys Glu Ala Pro
85 90 95
Gly Ser Cys Val Ala Val His Cys Val Ala Gly Leu Gly Arg Ala Pro
100 105 110
Val Leu Val Ala Leu Ala Leu Ile Glu Ser Gly Met Lys Tyr Glu Asp
115 120 125
Ala Ile Gln Phe Ile Arg Gln Lys Arg Arg Gly Ala Ile Asn Ser Lys
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Gln Leu Thr Tyr Leu Glu Lys Tyr Arg Pro Lys Gln Arg Leu Arg Phe
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Lys Asp Pro His Thr His Lys Thr Arg Cys Cys Val Met
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<212> DNA
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<400> 249

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<210> 250
<211> 1179
<212> PRT
<213> Homo sapiens

<400> 250
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35 40 45
Tyr Thr Val Gln Gln Tyr Glu Asn Glu Glu Gly Lys Trp Val Leu Ile
50 55 60
Gly Ser Pro Leu Val Gly Gln Pro Lys Asn Arg Thr Gly Asp Val Tyr
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Lys Cys Pro Val Gly Arg Gly Glu Ser Leu Pro Cys Val Lys Leu Asp
85 90 95
Leu Pro Val Asn Thr Ser Ile Pro Asn Val Thr Glu Val Lys Glu Asn
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Met Thr Phe Gly Ser Thr Leu Val Thr Asn Pro Asn Gly Gly Phe Leu
115 120 125
Ala Cys Gly Pro Leu Tyr Ala Tyr Arg Cys Gly His Leu His Tyr Thr
130 135 140
Thr Gly Ile Cys Ser Asp Val Ser Pro Thr Phe Gln Val Val Asn Ser

145 150 155 160
Ile Ala Pro Val Gln Glu Cys Ser Thr Gln Leu Asp Ile Val Ile Val
165 170 175
Leu Asp Gly Ser Asn Ser Ile Tyr Pro Trp Asp Ser Val Thr Ala Phe
180 185 190
Leu Asn Asp Leu Leu Lys Arg Met Asp Ile Gly Pro Lys Gln Thr Gln
195 200 205
Val Gly Ile Val Gln Tyr Gly Glu Asn Val Thr His Glu Phe Asn Leu
210 215 220
Asn Lys Tyr Ser Ser Thr Glu Glu Val Leu Val Ala Ala Lys Lys Ile
225 230 235 240
Val Gln Arg Gly Gly Arg Gln Thr Met Thr Ala Leu Gly Thr Asp Thr
245 250 255
Ala Arg Lys Glu Ala Phe Thr Glu Ala Arg Gly Ala Arg Arg Gly Val
260 265 270
Lys Lys Val Met Val Ile Val Thr Asp Gly Glu Ser His Asp Asn His
275 280 285
Arg Leu Lys Lys Val Ile Gln Asp Cys Glu Asp Glu Asn Ile Gln Arg
290 295 300
Phe Ser Ile Ala Ile Leu Gly Ser Tyr Asn Arg Gly Asn Leu Ser Thr
305 310 315 320
Glu Lys Phe Val Glu Glu Ile Lys Ser Ile Ala Ser Glu Pro Thr Glu
325 330 335
Lys His Phe Phe Asn Val Ser Asp Glu Leu Ala Leu Val Thr Ile Val
340 345 350
Lys Thr Leu Gly Glu Arg Ile Phe Ala Leu Glu Ala Thr Ala Asp Gln
355 360 365
Ser Ala Ala Ser Phe Glu Met Glu Met Ser Gln Thr Gly Phe Ser Ala
370 375 380
His Tyr Ser Gln Asp Trp Val Met Leu Gly Ala Val Gly Ala Tyr Asp
385 390 395 400
Trp Asn Gly Thr Val Val Met Gln Lys Ala Ser Gln Ile Ile Ile Pro
405 410 415
Arg Asn Thr Thr Phe Asn Val Glu Ser Thr Lys Lys Asn Glu Pro Leu
420 425 430
Ala Ser Tyr Leu Gly Tyr Thr Val Asn Ser Ala Thr Ala Ser Ser Gly
435 440 445
Asp Val Leu Tyr Ile Ala Gly Gln Pro Arg Tyr Asn His Thr Gly Gln
450 455 460
Val Ile Ile Tyr Arg Met Glu Asp Gly Asn Ile Lys Ile Leu Gln Thr
465 470 475 480
Leu Ser Gly Glu Gln Ile Gly Ser Tyr Phe Gly Ser Ile Leu Thr Thr
485 490 495
Thr Asp Ile Asp Lys Asp Ser Asn Thr Asp Ile Leu Leu Val Gly Ala
500 505 510
Pro Met Tyr Met Gly Thr Glu Lys Glu Glu Gln Gly Lys Val Tyr Val
515 520 525
Tyr Ala Leu Asn Gln Thr Arg Phe Glu Tyr Gln Met Ser Leu Glu Pro
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545 550 555 560
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565 570 575
Ala Val Lys Asp Leu Asn Leu Asp Gly Phe Asn Asp Ile Val Ile Gly
580 585 590
Ala Pro Leu Glu Asp Asp His Gly Gly Ala Val Tyr Ile Tyr His Gly
595 600 605
Ser Gly Lys Thr Ile Arg Lys Glu Tyr Ala Gln Arg Ile Pro Ser Gly
610 615 620
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625 630 635 640

Met Asp Leu Asn Gly Asp Gly Leu Thr Asp Val Thr Ile Gly Gly Leu
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675 680 685
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725 730 735
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Lys Ser Glu Cys Thr Lys His Ser Phe Tyr Met Leu Asp Lys His Asp
755 760 765
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Glu Asn Gly Pro Val Leu Asp Asp Ser Leu Pro Asn Ser Val His Glu
785 790 795 800
Tyr Ile Pro Phe Ala Lys Asp Cys Gly Asn Lys Glu Lys Cys Ile Ser
805 810 815
Asp Leu Ser Leu His Val Ala Thr Thr Glu Lys Asp Leu Leu Ile Val
820 825 830
Arg Ser Gln Asn Asp Lys Phe Asn Val Ser Leu Thr Val Lys Asn Thr
835 840 845
Lys Asp Ser Ala Tyr Asn Thr Arg Thr Ile Val His Tyr Ser Pro Asn
850 855 860
Leu Val Phe Ser Gly Ile Glu Ala Ile Gln Lys Asp Ser Cys Glu Ser
865 870 875 880
Asn His Asn Ile Thr Cys Lys Val Gly Tyr Pro Phe Leu Arg Arg Gly
885 890 895
Glu Met Val Thr Phe Lys Ile Leu Phe Gln Phe Asn Thr Ser Tyr Leu
900 905 910
Met Glu Asn Val Thr Ile Tyr Leu Ser Ala Thr Ser Asp Ser Glu Glu
915 920 925
Pro Pro Glu Thr Leu Ser Asp Asn Val Val Asn Ile Ser Ile Pro Val
930 935 940
Lys Tyr Glu Val Gly Leu Gln Phe Tyr Ser Ser Ala Ser Glu Tyr His
945 950 955 960
Ile Ser Ile Ala Ala Asn Glu Thr Val Pro Glu Val Ile Asn Ser Thr
965 970 975
Glu Asp Ile Gly Asn Glu Ile Asn Ile Phe Tyr Leu Ile Arg Lys Ser
980 985 990
Gly Ser Phe Pro Met Pro Glu Leu Lys Leu Ser Ile Ser Phe Pro Asn
995 1000 1005
Met Thr Ser Asn Gly Tyr Pro Val Leu Tyr Pro Thr Gly Leu Ser Ser
1010 1015 1020
Ser Glu Asn Ala Asn Cys Arg Pro His Ile Phe Glu Asp Pro Phe Ser
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Gly Thr Ile Leu Asp Cys Asn Thr Cys Lys Phe Ala Thr Ile Thr Cys
1060 1065 1070
Asn Leu Thr Ser Ser Asp Ile Ser Gln Val Asn Val Ser Leu Ile Leu
1075 1080 1085
Trp Lys Pro Thr Phe Ile Lys Ser Tyr Phe Ser Ser Leu Asn Leu Thr
1090 1095 1100
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Ser Asn Gln Lys Arg Glu Leu Ala Ile Gln Ile Ser Lys Asp Gly Leu

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Gly Glu Arg Gly Leu Pro Gly Leu Gln Gly Val Ile Gly Phe Pro Gly
    50                  55                  60
Met Gln Gly Pro Glu Gly Pro Gln Gly Pro Pro Gly Gln Lys Gly Asp
65                  70                  75                  80
Thr Gly Glu Pro Gly Leu Pro Gly Thr Lys Gly Thr Arg Gly Pro Pro
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Gly Ala Ser Gly Tyr Pro Gly Asn Pro Gly Leu Pro Gly Ile Pro Gly
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Gln Asp Gly Pro Pro Gly Pro Pro Gly Ile Pro Gly Cys Asn Gly Thr
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Glu Ile Leu Gly His Val Pro Gly Met Leu Leu Lys Gly Glu Arg Gly
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Phe Pro Gly Ile Pro Gly Thr Pro Gly Pro Pro Gly Leu Pro Gly Leu
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Gln Gly Pro Val Gly Pro Pro Gly Phe Thr Gly Pro Pro Gly Pro Pro
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Gln Gly Pro Lys Gly Asp Lys Gly Asp Gln Gly Val Ser Gly Pro Pro
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Lys Gly Glu Lys Gly Gln Lys Gly Glu Pro Gly Phe Gln Gly Met Pro
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Pro Gly Lys Asp Gly Asp Lys Gly Glu Lys Gly Ser Pro Gly Phe Pro
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Gly Glu Pro Gly Tyr Pro Gly Leu Ile Gly Arg Gln Gly Pro Gln Gly
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Glu Lys Gly Glu Ala Gly Pro Pro Gly Pro Pro Gly Ile Val Ile Gly
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Thr Gly Pro Leu Gly Glu Lys Gly Glu Arg Gly Tyr Pro Gly Thr Pro
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Gly Pro Arg Gly Glu Pro Gly Pro Lys Gly Phe Pro Gly Leu Pro Gly
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Gln Pro Gly Pro Pro Gly Leu Pro Val Pro Gly Gln Ala Gly Ala Pro
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Gly Phe Pro Gly Glu Arg Gly Glu Lys Gly Asp Arg Gly Phe Pro Gly
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Glu Ser Cys Leu Ile Cys Asp Ile Asp Gly Tyr Arg Gly Pro Pro Gly
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485 490 495
Lys Gly Asp Arg Gly Leu Pro Gly Arg Asp Gly Val Ala Gly Val Pro
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Gly Pro Gln Gly Thr Pro Gly Leu Ile Gly Gln Pro Gly Ala Lys Gly
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Glu Pro Gly Glu Phe Tyr Phe Asp Leu Arg Leu Lys Gly Asp Lys Gly
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Phe Pro Gly Ser Arg Gly Asp Thr Gly Pro Pro Gly Pro Pro Gly Tyr
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Thr Pro Gly Glu Lys Gly Ser Ile Gly Val Pro Gly Val Pro Gly Glu
755 760 765
His Gly Ala Ile Gly Pro Pro Gly Leu Gln Gly Ile Arg Gly Glu Pro
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Gly Pro Pro Gly Leu Pro Gly Ser Val Gly Ser Pro Gly Val Pro Gly
785 790 795 800
Ile Gly Pro Pro Gly Ala Arg Gly Pro Pro Gly Gly Gln Gly Pro Pro
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Phe Pro Gly Leu Asp Met Pro Gly Pro Lys Gly Asp Lys Gly Ala Gln
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Ser Met Lys Gly Gln Lys Gly Asp Gln Gly Glu Lys Gly Gln Ile Gly
945 950 955 960
Pro Ile Gly Glu Lys Gly Ser Arg Gly Asp Pro Gly Thr Pro Gly Val
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Pro Gly Lys Asp Gly Gln Ala Gly Gln Pro Gly Gln Pro Gly Pro Lys
980 985 990
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35 40 45
Lys Gln Leu Lys Gly Lys Asn Pro Glu Asp Leu Ile Trp His Thr Pro
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Lys Ile Phe Val Pro Ser Lys Gly Ser Arg Ser Asn Val Pro Lys Val
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Ala Ile Lys Leu Arg Asn Ser Asp Val Glu Ile Phe Ala Val Gly Val
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Lys Asp Ala Val Arg Ser Glu Leu Glu Ala Ile Ala Ser Pro Pro Ala
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Glu Thr His Val Phe Thr Val Glu Asp Phe Asp Ala Phe Gln Arg Ile
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Ser Phe Glu Leu Thr Gln Ser Ile Cys Leu Arg Ile Glu Gln Glu Leu
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Ala Ala Ile Lys Lys Lys Ala Tyr Val Pro Pro Lys Asp Leu Ser Phe
625 630 635 640
Ser Glu Val Thr Ser Tyr Gly Phe Lys Thr Asn Trp Ser Pro Ala Gly
645 650 655
Glu Asn Val Phe Ser Tyr His Ile Thr Tyr Lys Glu Ala Ala Gly Asp
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Asp Glu Val Thr Val Val Glu Pro Ala Ser Ser Thr Ser Val Val Leu
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Tyr Glu Asp Gly Phe Ser Ile Pro Leu Ala Gly Glu Glu Thr Thr Glu
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Glu Val Lys Gly Ala Pro Arg Asn Leu Lys Val Thr Asp Glu Thr Thr
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740 745 750
Cys Arg Ile Ile Tyr Arg Pro Val Ala Gly Gly Glu Ser Arg Glu Val
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Asp Thr Lys Tyr Glu Val Ser Val Ile Pro Glu Tyr Phe Ser Gly Pro
785 790 795 800
Gly Thr Pro Leu Thr Gly Asn Ala Ala Thr Glu Glu Val Arg Gly Asn
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Tyr Lys Val Asn Val Phe Gly Met Phe Asp Gly Gly Glu Ser Ser Pro
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1265 1270 1275 1280
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1315 1320 1325
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1330 1335 1340
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1345 1350 1355 1360
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1365 1370 1375
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1425 1430 1435 1440
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1445 1450 1455
Val Val Glu Asp Glu Tyr Ser Glu Pro Leu Lys Gly Thr Glu Lys Thr
1460 1465 1470
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1475 1480 1485
Thr Met His Val Gln Trp Gln Pro Val Gly Gly Ala Thr Gly Tyr Ile
1490 1495 1500
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1940 1945 1950
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1955 1960 1965
Ser Pro Val Asp Gly Thr Arg Pro Ser Glu Ser Ile Val Val Pro Gly
1970 1975 1980
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1985 1990 1995 2000
Ser Val Asn Leu Val Ala Leu Tyr Ser Asp Gly Glu Gly Asn Pro Ser
2005 2010 2015

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His Cys Phe Thr Gly Leu Ser Pro Asp Thr Asp Tyr Gly Val Thr Val
2260 2265 2270
Phe Val Gln Thr Pro Asn Leu Glu Gly Pro Gly Val Ser Val Lys Glu
2275 2280 2285
His Thr Thr Val Lys Pro Thr Glu Ala Pro Thr Glu Pro Pro Thr Pro
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2660 2665 2670
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Ser Arg Thr Gly Pro Pro Gly Ser Thr Gly Ser Arg Gly Pro Pro Gly
3010 3015 3020
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Ser Ala Met Tyr Cys Asp Glu Leu Lys Leu Lys Ser Val Pro Met Val
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Pro Pro Gly Ile Lys Tyr Leu Tyr Leu Arg Asn Asn Gln Ile Asp His
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Ile Asp Glu Lys Ala Phe Glu Asn Val Thr Asp Leu Gln Trp Leu Ile
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Leu Asp His Asn Leu Leu Glu Asn Ser Lys Ile Lys Gly Arg Val Phe
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Ser Lys Leu Lys Gln Leu Lys Lys Leu His Ile Asn His Asn Asn Leu
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145 150 155 160
Leu Thr Phe Ile His Leu Gln His Asn Arg Leu Lys Glu Asp Ala Val
165 170 175
Ser Ala Ala Phe Lys Gly Leu Lys Ser Leu Glu Tyr Leu Asp Leu Ser
180 185 190
Phe Asn Gln Ile Ala Arg Leu Pro Ser Gly Leu Pro Val Ser Leu Leu
195 200 205
Thr Leu Tyr Leu Asp Asn Asn Lys Ile Ser Asn Ile Pro Asp Glu Tyr
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Phe Lys Arg Phe Asn Ala Leu Gln Tyr Leu Arg Leu Ser His Asn Glu
225 230 235 240
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245 250 255
Val Glu Leu Asp Leu Ser Tyr Asn Lys Leu Lys Asn Ile Pro Thr Val
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Asn Glu Asn Leu Glu Asn Tyr Tyr Leu Glu Val Asn Gln Leu Glu Lys
275 280 285
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Pro Gly Ala Pro Gly Pro Gln Gly Phe Gln Gly Pro Pro Gly Glu Pro
195 200 205
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210 215 220
Pro Pro Gly Lys Asn Gly Asp Asp Gly Glu Ala Gly Lys Pro Gly Arg
225 230 235 240
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Pro Gly Ser Pro Gly Glu Asn Gly Ala Pro Gly Gln Met Gly Pro Arg
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690 695 700
Asn Asp Gly Ala Lys Gly Asp Ala Gly Ala Pro Gly Ala Pro Gly Ser
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Gln Gly Ala Pro Gly Leu Gln Gly Met Pro Gly Glu Arg Gly Ala Ala
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Val Pro Tyr Gln Val Leu Ala Leu Tyr Asn Ser Thr Arg Glu Leu Leu
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Glu Ser Glu Tyr Tyr Ala Lys Glu Ile His Lys Phe Asp Met Ile Gln
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Ile His Cys Pro Cys His Thr Phe Gln Pro Asn Gly Asp Ile Leu Glu
225                 230                 235                 240
Asn Ile His Glu Val Met Glu Ile Lys Phe Lys Gly Val Asp Asn Glu
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Asp Asp His Gly Arg Gly Asp Leu Gly Arg Leu Lys Lys Gln Lys Asp
            260                 265                 270
His His Asn Pro His Leu Ile Leu Met Met Ile Pro Pro His Arg Leu
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Lys Gly Tyr Tyr Ala Asn Phe Cys Ser Gly Pro Cys Pro Tyr Leu Arg
            340                 345                 350
Ser Ala Asp Thr Thr His Ser Thr Val Leu Gly Leu Tyr Asn Thr Leu
        355                 360                 365
Asn Pro Glu Ala Ser Ala Ser Pro Cys Cys Val Pro Gln Asp Leu Glu
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35 40 45
Pro Pro Gly Arg Asp Gly Glu Asp Gly Pro Thr Gly Pro Pro Gly Pro
50 55 60
Pro Gly Pro Pro Gly Pro Pro Gly Leu Gly Gly Asn Phe Ala Ala Gln
65 70 75 80
Tyr Asp Gly Lys Gly Val Gly Leu Gly Pro Gly Pro Met Gly Leu Met
85 90 95
Gly Pro Arg Gly Pro Pro Gly Ala Ala Gly Ala Pro Gly Pro Gln Gly
100 105 110
Phe Gln Gly Pro Ala Gly Glu Pro Gly Glu Pro Gly Gln Thr Gly Pro
115 120 125
Ala Gly Ala Arg Gly Pro Ala Gly Pro Pro Gly Lys Ala Gly Glu Asp
130 135 140
Gly His Pro Gly Lys Pro Gly Arg Pro Gly Glu Arg Gly Val Val Gly
145 150 155 160
Pro Gln Gly Ala Arg Gly Phe Pro Gly Thr Pro Gly Leu Pro Gly Phe
165 170 175
Lys Gly Ile Arg Gly His Asn Gly Leu Asp Gly Leu Lys Gly Gln Pro
180 185 190
Gly Ala Pro Gly Val Lys Gly Glu Pro Gly Ala Pro Gly Glu Asn Gly
195 200 205
Thr Pro Gly Gln Thr Gly Ala Arg Gly Leu Pro Gly Glu Arg Gly Arg
210 215 220
Val Gly Ala Pro Gly Pro Ala Gly Ala Arg Gly Ser Asp Gly Ser Val
225 230 235 240
Gly Pro Val Gly Pro Ala Gly Pro Ile Gly Ser Ala Gly Pro Pro Gly
245 250 255
Phe Pro Gly Ala Pro Gly Pro Lys Gly Glu Ile Gly Ala Val Gly Asn
260 265 270
Ala Gly Pro Ala Gly Pro Ala Gly Pro Arg Gly Glu Val Gly Leu Pro
275 280 285
Gly Leu Ser Gly Pro Val Gly Pro Pro Gly Asn Pro Gly Ala Asn Gly
290 295 300
Leu Thr Gly Ala Lys Gly Ala Ala Gly Leu Pro Gly Val Ala Gly Ala
305 310 315 320
Pro Gly Leu Pro Gly Pro Arg Gly Ile Pro Gly Pro Val Gly Ala Ala
325 330 335
Gly Ala Thr Gly Ala Arg Gly Leu Val Gly Glu Pro Gly Pro Ala Gly
340 345 350
Ser Lys Gly Glu Ser Gly Asn Lys Gly Glu Pro Gly Ser Ala Gly Pro
355 360 365

Gln Gly Pro Pro Gly Pro Ser Gly Glu Glu Gly Lys Arg Gly Pro Asn
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Gly Glu Ala Gly Ser Ala Gly Pro Pro Gly Pro Pro Gly Leu Arg Gly
385 390 395 400
Ser Pro Gly Ser Arg Gly Leu Pro Gly Ala Asp Gly Arg Ala Gly Val
405 410 415
Met Gly Pro Pro Gly Ser Arg Gly Ala Ser Gly Pro Ala Gly Val Arg
420 425 430
Gly Pro Asn Gly Asp Ala Gly Arg Pro Gly Glu Pro Gly Leu Met Gly
435 440 445
Pro Arg Gly Leu Pro Gly Ser Pro Gly Asn Ile Gly Pro Ala Gly Lys
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465 470 475 480
Gly Pro Ala Gly Ala Arg Gly Glu Pro Gly Asn Ile Gly Phe Pro Gly
485 490 495
Pro Lys Gly Pro Thr Gly Asp Pro Gly Lys Asn Gly Asp Lys Gly His
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Ala Gly Leu Ala Gly Ala Arg Gly Ala Pro Gly Pro Asp Gly Asn Asn
515 520 525
Gly Ala Gln Gly Pro Pro Gly Pro Gln Gly Val Gln Gly Gly Lys Gly
530 535 540
Glu Gln Gly Pro Ala Gly Pro Pro Gly Phe Gln Gly Leu Pro Gly Pro
545 550 555 560
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Gly Glu Phe Gly Leu Pro Gly Pro Ala Gly Pro Arg Gly Glu Arg Gly
580 585 590
Pro Pro Gly Glu Ser Gly Ala Ala Gly Pro Thr Gly Pro Ile Gly Ser
595 600 605
Arg Gly Pro Ser Gly Pro Pro Gly Pro Asp Gly Asn Lys Gly Glu Pro
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Leu Pro Gly Glu Arg Gly Ala Ala Gly Ile Pro Gly Gly Lys Gly Glu
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Lys Gly Glu Pro Gly Leu Arg Gly Glu Ile Gly Asn Pro Gly Arg Asp
660 665 670
Gly Ala Arg Gly Ala His Gly Ala Val Gly Ala Pro Gly Pro Ala Gly
675 680 685
Ala Thr Gly Asp Arg Gly Glu Ala Gly Ala Ala Gly Pro Ala Gly Pro
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Ala Gly Pro Arg Gly Ser Pro Gly Glu Arg Gly Glu Val Gly Pro Ala
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Gly Pro Asn Gly Phe Ala Gly Pro Ala Gly Ala Ala Gly Gln Pro Gly
725 730 735
Ala Lys Gly Glu Arg Gly Ala Lys Gly Pro Lys Gly Glu Asn Gly Val
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Val Gly Pro Thr Gly Pro Val Gly Ala Ala Gly Pro Ala Gly Pro Asn
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Met Thr Gly Phe Pro Gly Ala Ala Gly Arg Thr Gly Pro Pro Gly Pro
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Ser Gly Ile Ser Gly Pro Pro Gly Pro Pro Gly Pro Ala Gly Lys Glu
805 810 815
Gly Leu Arg Gly Pro Arg Gly Asp Gln Gly Pro Val Gly Arg Thr Gly
820 825 830
Glu Val Gly Ala Val Gly Pro Pro Gly Phe Ala Gly Glu Lys Gly Pro
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Ser Gly Glu Ala Gly Thr Ala Gly Pro Pro Gly Thr Pro Gly Pro Gln

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Glu Arg Gly Leu Pro Gly Val Ala Gly Ala Val Gly Glu Pro Gly Pro
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Gly Ser Pro Gly Val Asn Gly Ala Pro Gly Glu Ala Gly Arg Asp Gly
915 920 925
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930 935 940
Lys Gly Glu Arg Gly Tyr Pro Gly Asn Ile Gly Pro Val Gly Ala Ala
945 950 955 960
Gly Ala Pro Gly Pro His Gly Pro Val Gly Pro Ala Gly Lys His Gly
965 970 975
Asn Arg Gly Glu Thr Gly Pro Ser Gly Pro Val Gly Pro Ala Gly Ala
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Val Gly Pro Arg Gly Pro Ser Gly Pro Gln Gly Ile Arg Gly Asp Lys
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Gly Glu Pro Gly Glu Lys Gly Pro Arg Gly Leu Pro Gly Leu Lys Gly
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Thr Val Gly Pro Ala Gly Ile Arg Gly Pro Gln Gly His Gln Gly Pro
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Ala Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Val Ser
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Gly Gly Gly Tyr Asp Phe Gly Tyr Asp Gly Asp Phe Tyr Arg Ala Asp
1105 1110 1115 1120
Gln Pro Arg Ser Ala Pro Ser Leu Arg Pro Lys Asp Tyr Glu Val Asp
1125 1130 1135
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Glu Gly Ser Arg Lys Asn Pro Ala Arg Thr Cys Arg Asp Leu Arg Leu
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1235 1240 1245
Glu Met Ala Thr Gln Leu Ala Phe Met Arg Leu Leu Ala Asn Tyr Ala
1250 1255 1260
Ser Gln Asn Ile Thr Tyr His Cys Lys Asn Ser Ile Ala Tyr Met Asp
1265 1270 1275 1280
Glu Glu Thr Gly Asn Leu Lys Lys Ala Val Ile Leu Gln Gly Ser Asn
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Asp Val Glu Leu Val Ala Glu Gly Asn Ser Arg Phe Thr Tyr Thr Val
1300 1305 1310
Leu Val Asp Gly Cys Ser Lys Lys Thr Asn Glu Trp Gly Lys Thr Ile
1315 1320 1325
Ile Glu Tyr Lys Thr Asn Lys Pro Ser Arg Leu Pro Phe Leu Asp Ile
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<213> Homo sapiens

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Cys Pro Pro Gln Gln Val Phe Gly Asp Leu Asp Gln Val Arg Met Thr
50 55 60
Ser Glu Gly Ser Asp Cys Arg Cys Lys Cys Ile Met Arg Pro Leu Ser

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Lys Asp Ala Cys Ser Arg Val Arg Ser Gly Arg Ala Arg Val Glu Asp
85 90 95
Phe Tyr Thr Val Glu Thr Val Ser Ser Gly Thr Asp Cys Arg Cys Ser
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Cys Thr Ala Pro Pro Ser Ser Leu Asn Pro Cys Glu Asn Glu Trp Lys
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130 135 140
Met Val Asp Leu Leu Glu Gly Thr Leu Tyr Ser Met Asp Leu Met Lys
145 150 155 160
Val His Ala Tyr Val His Lys Val Ala Ser Gln Met Asn Thr Leu Glu
165 170 175
Glu Ser Ile Lys Ala Asn Leu Ser Arg Glu Asn Glu Val Val Lys Asp
180 185 190
Ser Val Arg His Leu Ser Glu Gln Leu Arg His Tyr Glu Asn His Ser
195 200 205
Ala Ile Met Leu Gly Ile Lys Lys Glu Leu Ser Arg Leu Gly Leu Gln
210 215 220
Leu Leu Gln Lys Asp Ala Ala Ala Ala Pro Ala Thr Pro Ala Thr Gly
225 230 235 240
Thr Gly Ser Lys Ala Gln Asp Thr Ala Arg Gly Lys Gly Lys Asp Ile
245 250 255
Ser Lys Tyr Gly Ser Val Gln Lys Ser Phe Ala Asp Arg Gly Leu Pro
260 265 270
Lys Pro Pro Lys Glu Lys Leu Leu Gln Val Glu Lys Leu Arg Lys Glu
275 280 285
Ser Gly Lys Gly Ser Phe Leu Gln Pro Thr Ala Lys Pro Arg Ala Leu
290 295 300
Ala Gln Gln Gln Ala Val Ile Arg Gly Phe Thr Tyr Tyr Lys Ala Gly
305 310 315 320
Lys Gln Glu Val Thr Glu Ala Val Ala Asp Asn Thr Leu Gln Gly Thr
325 330 335
Ser Trp Leu Glu Gln Leu Pro Pro Lys Val Glu Gly Arg Ser Asn Ser
340 345 350
Ala Glu Pro Asn Ser Ala Glu Gln Asp Glu Ala Glu Pro Arg Ser Ser
355 360 365
Glu Arg Val Asp Leu Ala Ser Gly Thr Pro Thr Ser Ile Pro Ala Thr
370 375 380
Thr Thr Thr Ala Thr Thr Thr Pro Thr Pro Thr Thr Ser Leu Leu Pro
385 390 395 400
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405 410 415
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420 425 430
Ser Tyr Gly Arg His Glu Gly Ala Trp Met Lys Asp Pro Ala Ala Arg
435 440 445
Asp Asp Arg Ile Tyr Val Thr Asn Tyr Tyr Tyr Gly Asn Ser Leu Val
450 455 460
Glu Phe Arg Asn Leu Glu Asn Phe Lys Gln Gly Arg Trp Ser Asn Met
465 470 475 480
Tyr Lys Leu Pro Tyr Asn Trp Ile Gly Thr Gly His Val Val Tyr Gln
485 490 495
Gly Ala Phe Tyr Tyr Asn Arg Ala Phe Thr Lys Asn Ile Ile Lys Tyr
500 505 510
Asp Leu Arg Gln Arg Phe Val Ala Ser Trp Ala Leu Leu Pro Asp Val
515 520 525
Val Tyr Glu Asp Thr Thr Pro Trp Lys Trp Arg Gly His Ser Asp Ile
530 535 540
Asp Phe Ala Val Asp Glu Ser Gly Leu Trp Val Ile Tyr Pro Ala Val
545 550 555 560

Asp Asp Arg Asp Glu Ala Gln Pro Glu Val Ile Val Leu Ser Arg Leu
565 570 575
Asp Pro Gly Asp Leu Ser Val His Arg Glu Thr Thr Trp Lys Thr Arg
580 585 590
Leu Arg Arg Asn Ser Tyr Gly Asn Cys Phe Leu Val Cys Gly Ile Leu
595 600 605
Tyr Ala Val Asp Thr Tyr Asn Gln Gln Glu Gly Gln Val Ala Tyr Ala
610 615 620
Phe Asp Thr His Thr Gly Thr Asp Ala Arg Pro Gln Leu Pro Phe Leu
625 630 635 640
Asn Glu His Ala Tyr Thr Thr Gln Ile Asp Tyr Asn Pro Lys Glu Arg
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<213> Homo sapiens

<400> 268
gacacctttt aaaatgcaga actaactgag gcatttcagt aactttgctt tcaaatcaat 60
aaagtcaaat gtatggaaac attttgtgcc ctactctcca taccctgtgt actcaaattc 120
tctactgtat gaattatgct ttaagtagaa ttcagtgcca aggagaactt ggtgaaataa 180
attattttaa tttttttttt atcctttaca aagccatgga ttttatttgg ttgatgtgtg 240
ctctgtacac aagccatttc aataggatgg agctgttaat tattttccaa agagtaatag 300
acatgcaaaa gtttcaataa aaactgggcc attaacaaat aaattaataa actaataagc 360
attcccttct aggtttttgc caaactgcct atccaataac aaatttgaga atcgttgaaa 420
aagctagtta tatttcagag aaatgatttt cattattgaa actgttctcc ctagcaggcc 480
attttccctt tttcctggga gtttagcaag tttaggagag aatagtcatg aaaagaaagg 540
gaagaaaggg gagaagggaa gaggttaaaa agtaagtgct cagacctatg aacgtaatcc 600
ctttgctaga aatatttaag agcagctcag cttggttgaa actgagtttt gtcatcttcc 660
atatttgcag gaaggtattt tctgacttgc aatgcagcta gatgtaaaat tttattttat 720
catcctagaa agccttgact agaaaaatga ataaatattg agggtttcct gtccatatct 780
ggcttgcatg tgccagaaag cagagaatag aaaatgtaat ctccaacatc caagcatcga 840
aacccaaggg gtaggcaatt ctatgtaggt tttggacatg aagtttggtg catcttggtt 900
tatgctggct caactgctat taaacctctc tggcttatag tctcttcatt ctattagaca 960
agcacgtatc gaacacttgc ttcgcacaag gctctttagt taacaattta gcagctactg 1020
tttgtgttaa acacactttt caccaaatag gttctgaggc aaacgagagc aatgactatt 1080
taaagaaagg ctttcccagc atcacttaca catcccaaaa ctaaaaagat caactcttcc 1140
aactgagaaa agactcctgg ctttgaatgg aaacttacag cagagagtca caggccacgg 1200
caacaacaac gacaacaaca aacatttgga atattattct caactcacgt tttaataata 1260
catcttaatt atttttctag tagagaaact acaaatcagc ctcttcaaca tttatataca 1320
gtttaataag cctcttgcaa gttacttgtt ctctcacctg aggtattttt ttcctcccca 1380
ccttgcccct gttcctccct tcctcttctc cctttgcaag aggaaatatt taacatattt 1440
gggtccaact tcaataatgt aataattaat acattaaaag catttaactt cctttctaga 1500
aaaatgcaca ggctaaggca tagacaaaac aaagagaaat gctgagaaat ttgccactgg 1560
agacaagcaa tctgaataaa tatttgccaa aagttctttt tatgtcatat agtgtcagga 1620
tttgaaggag ctattttttt taatgttgca actagcaact catcttcgga agacacagcc 1680
aggagaatga agtagaagtg aaaggtttat aaatccattt gtaagcattt atcccatata 1740
ttttaaattc aagaaaaatt gtgtttatct ttagaatttt gtattcaata ctttatgtac 1800
tatgtgactc atgcttctgg ataaataaag caccaaatat gtatctgtaa ccacaatcac 1860
acatattata ttaaatatat atctatataa caaaaaaaaa aaaaaaaaa 1909

<210> 269
<211> 83
<212> PRT
<213> Homo sapiens

<400> 269
Met Tyr Gly Asn Ile Leu Cys Pro Thr Leu His Thr Leu Cys Thr Gln
1 5 10 15
Ile Leu Tyr Cys Met Asn Tyr Ala Leu Ser Arg Ile Gln Cys Gln Gly
20 25 30
Glu Leu Gly Glu Ile Asn Tyr Phe Asn Phe Phe Phe Ile Leu Tyr Lys
35 40 45
Ala Met Asp Phe Ile Trp Leu Met Cys Ala Leu Tyr Thr Ser His Phe
50 55 60
Asn Arg Met Glu Leu Leu Ile Ile Phe Gln Arg Val Ile Asp Met Gln
65 70 75 80
Lys Phe Gln

<210> 270
<211> 1720
<212> DNA
<213> Homo sapiens

<400> 270
gactgcagat gaaattagta actggtgggg tcgtggggtg tgaatggtgg gcgggagcag 60
ctatgtcagt tggtgtgttt ctgcttatgt tagggtaatt gggcacggcc tttgtgtaac 120
tggtgaatat ctctgaacct gggcatgaaa cagagagatg tcctaactct gggtgagagg 180
aatcctcatt tttctctgcc ctctcactgt ggcatcctaa gaaaaaagtt ttgggttcct 240
gcagcatgaa ggagagctct gctcccagaa tttgggagct ccagatttct tccagggtgt 300
ggaggcatca atatatcagt ctgggaaagg ggttcctggg ccactccagg agctgagttg 360
ggtggaaggt gctgagagtg tgggtggggg ccacttctga gcacccatgt ggcacccact 420
gctggtccct gtttgtggct gggcactcag gaaaatgttt ttggtgctaa gagtaaaaag 480
ccaaccaaca aacacatctc ttttttctgt ctattcactg gaaagtaaaa gcagtctggg 540
cgcaggctgg ggacccagat ggaattcaaa cttatgcctg ctctcaaggt gctcacggtt 600
gctgataaac agctggataa aatgaagagt ctatgagtga gggatgcaga gccagggaag 660
gctggtggag tgatgccacc agcacagggg tatgagtttg cagctgccaa ggggccaagg 720
gatgagctgg ggccctcctt cccaatggca tctccccctg gtctggaact gaagacactg 780
agcaatggtc cccaagcccc aaggagatca gctcccctgg gcccagtggc cccaaccagg 840
gagggtgtgg agaatgcctg cttctcctca gaggagcatg agacccattt ccagaaccct 900
gggaacacga gactgggcag ctcacccagt ccccctgggg gtgtctcctc actgccccga 960
tcccagcggg atgatctgtc ccttcattca gaggaggggc cagccctgga gcccgtgagc 1020
cgcccggtgg attatggctt tgtttccgcc ctcgttttcc tggtgagtgg gattcttctg 1080
gtggtgacag catacgccat cccccgtgag gctcgagtca atccggacac agtgacagcg 1140
cgggagatgg aacgactgga gatgtactac gcccgcctag gctcccacct ggacaggtgc 1200
atcatcgcag gcctcgggct gctcacggtg ggcggcatgc tcttgtcggt gctgctcatg 1260
gtctccctgt gcaagggcga gctgtaccgc cggaggacct tcgtccccgg caagggctcc 1320
aggaagacct acggctccat taacctgcgc atgagacagc tcaatgggga tgggggccag 1380
gccctggtgg agaatgaagt tgtccaggtc tcagagacta gccacacccct ccagaggtct 1440
taagaactag cccaccttat ctggctgctt tagctccagt gctacaaggt ccaccccctg 1500
ctcccgccca cctgacccct gccaaggccc tggggtttta aactgagctc acatagggcc 1560
ttgtggaaga agtactgggt gctggaggga gagctcgggg cccagcccat gccccacacg 1620
ggcaagcagc ccactgatct gttttgtagc tgaggttttg catacggttt tgtttggagg 1680
atggcttctg ctgctaaaaa tacaaaagtt tggaaaccgc 1720

<210> 271
<211> 256
<212> PRT
<213> Homo sapiens

<400> 271
Met Pro Pro Ala Gln Gly Tyr Glu Phe Ala Ala Ala Lys Gly Pro Arg
1 5 10 15
Asp Glu Leu Gly Pro Ser Phe Pro Met Ala Ser Pro Pro Gly Leu Glu
20 25 30
Leu Lys Thr Leu Ser Asn Gly Pro Gln Ala Pro Arg Arg Ser Ala Pro

35 40 45
Leu Gly Pro Val Ala Pro Thr Arg Glu Gly Val Glu Asn Ala Cys Phe
50 55 60
Ser Ser Glu Glu His Glu Thr His Phe Gln Asn Pro Gly Asn Thr Arg
65 70 75 80
Leu Gly Ser Ser Pro Ser Pro Pro Gly Gly Val Ser Ser Leu Pro Arg
85 90 95
Ser Gln Arg Asp Asp Leu Ser Leu His Ser Glu Glu Gly Pro Ala Leu
100 105 110
Glu Pro Val Ser Arg Pro Val Asp Tyr Gly Phe Val Ser Ala Leu Val
115 120 125
Phe Leu Val Ser Gly Ile Leu Leu Val Val Thr Ala Tyr Ala Ile Pro
130 135 140
Arg Glu Ala Arg Val Asn Pro Asp Thr Val Thr Ala Arg Glu Met Glu
145 150 155 160
Arg Leu Glu Met Tyr Tyr Ala Arg Leu Gly Ser His Leu Asp Arg Cys
165 170 175
Ile Ile Ala Gly Leu Gly Leu Leu Thr Val Gly Gly Met Leu Leu Ser
180 185 190
Val Leu Leu Met Val Ser Leu Cys Lys Gly Glu Leu Tyr Arg Arg Arg
195 200 205
Thr Phe Val Pro Gly Lys Gly Ser Arg Lys Thr Tyr Gly Ser Ile Asn
210 215 220
Leu Arg Met Arg Gln Leu Asn Gly Asp Gly Gly Gln Ala Leu Val Glu
225 230 235 240
Asn Glu Val Val Gln Val Ser Glu Thr Ser His Thr Leu Gln Arg Ser
245 250 255

<210> 272
<211> 1111
<212> DNA
<213> Homo sapiens

<400> 272
ccgcgcgctc gccccgccgc tcctgctgca gccccaggcc cctcgccgcc gccaccatgg 60
acgccatcaa gaagaagatg cagatgctga agctcgacaa ggagaacgcc ttggatcgag 120
ctgagcaggc ggaggccgac aagaaggcgg cggaagacag gagcaagcag ctggaagatg 180
agctggtgtc actgcaaaag aaactcaagg gcaccgaaga tgaactggac aaatactctg 240
aggctctcaa agatgcccag gagaagctgg agctggcaga gaaaaaggcc accgatgctg 300
aagccgacgt agcttctctg aacagacgca tccagctggt tgaggaagag ttggatcgtg 360
cccaggagcg tctggcaaca gctttgcaga agctggagga agctgagaag gcagcagatg 420
agagtgagag aggcatgaaa gtcattgaga gtcgagccca aaaagatgaa gaaaaaatgg 480
aaattcagga gatccaactg aaagaggcca agcacattgc tgaagatgcc gaccgcaaat 540
acgaagaggt ggcccgtaag ctggtcatca ttgagagcga cctggaacgt gcagaggagc 600
gggctgagct ctcagaaggc aaatgtgccg agcttgaaga agaattgaaa actgtgacga 660
acaacttgaa gtcactggag gctcaggctg agaagtactc gcagaaggaa gacagatatg 720
aggaagagat caaggtcctt tccgacaagc tgaaggaggc tgagactcgg gctgagtttg 780
cggagaggtc agtaactaaa ttggagaaaa gcattgatga cttagaagac gagctgtacg 840
ctcagaaact gaagtacaaa gccatcagcg aggagctgga ccacgctctc aacgatatga 900
cttccatata agtttctttg cttcacttct cccaagactc cctcgtcgag ctggatgtcc 960
cacctctctg agctctgcat ttgtctattc tccagctgac cctggttctc tctcttagca 1020
tcctgcctta gagccaggca cacactgtgc tttctattgt acagaagctc ttcgtttcag 1080
tgtcaaataa acactgtgta agctaaaaaa a 1111

<210> 273
<211> 284
<212> PRT
<213> Homo sapiens

<400> 273
Met Asp Ala Ile Lys Lys Lys Met Gln Met Leu Lys Leu Asp Lys Glu

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1               5                   10                  15
Asn Ala Leu Asp Arg Ala Glu Gln Ala Glu Ala Asp Lys Lys Ala Ala
            20                  25                  30
Glu Asp Arg Ser Lys Gln Leu Glu Asp Glu Leu Val Ser Leu Gln Lys
        35                  40                  45
Lys Leu Lys Gly Thr Glu Asp Glu Leu Asp Lys Tyr Ser Glu Ala Leu
    50                  55                  60
Lys Asp Ala Gln Glu Lys Leu Glu Leu Ala Glu Lys Lys Ala Thr Asp
65                  70                  75                  80
Ala Glu Ala Asp Val Ala Ser Leu Asn Arg Arg Ile Gln Leu Val Glu
                85                  90                  95
Glu Glu Leu Asp Arg Ala Gln Glu Arg Leu Ala Thr Ala Leu Gln Lys
            100                 105                 110
Leu Glu Glu Ala Glu Lys Ala Ala Asp Glu Ser Glu Arg Gly Met Lys
        115                 120                 125
Val Ile Glu Ser Arg Ala Gln Lys Asp Glu Glu Lys Met Glu Ile Gln
    130                 135                 140
Glu Ile Gln Leu Lys Glu Ala Lys His Ile Ala Glu Asp Ala Asp Arg
145                 150                 155                 160
Lys Tyr Glu Glu Val Ala Arg Lys Leu Val Ile Ile Glu Ser Asp Leu
                165                 170                 175
Glu Arg Ala Glu Glu Arg Ala Glu Leu Ser Glu Gly Lys Cys Ala Glu
            180                 185                 190
Leu Glu Glu Glu Leu Lys Thr Val Thr Asn Asn Leu Lys Ser Leu Glu
        195                 200                 205
Ala Gln Ala Glu Lys Tyr Ser Gln Lys Glu Asp Arg Tyr Glu Glu Glu
    210                 215                 220
Ile Lys Val Leu Ser Asp Lys Leu Lys Glu Ala Glu Thr Arg Ala Glu
225                 230                 235                 240
Phe Ala Glu Arg Ser Val Thr Lys Leu Glu Lys Ser Ile Asp Asp Leu
                245                 250                 255
Glu Asp Glu Leu Tyr Ala Gln Lys Leu Lys Tyr Lys Ala Ile Ser Glu
            260                 265                 270
Glu Leu Asp His Ala Leu Asn Asp Met Thr Ser Ile
        275                 280
```

<210> 274
<211> 2032
<212> DNA
<213> Homo sapiens

<400> 274

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caccccgcag cccggcctcg gcctccgccg cttgttgtcg cgccccgccc gcgagcccgc     60
cccgcacgtc ccccgccggc ggccaccatg agcacaggcc tgcggtacaa gagcaagctg    120
gcgaccccag aggacaagca ggacattgac aagcagtacg tgggcttcgc cacactgccc    180
aaccaggtgc accgcaagtc ggtgaagaaa ggctttgact tcacactcat ggtggctggt    240
gagtcaggcc tggggaagtc cacactggtc cacagcctct tcctgacaga cttgtacaag    300
gaccggaagc tgctcagtgc tgaggagcgc atcagccaga cggtagagat tctaaaacac    360
acggtggaca ttgaggagaa gggagtcaag ctgaagctca ccatcgtgga cacgccggga    420
ttcggggacg ctgtcaacaa caccgagtgc tggaagccca tcaccgacta tgtggaccag    480
cagtttgagc agtacttccg tgatgagagc ggcctcaacc gaaagaacat ccaagacaac    540
cgagtgcact gctgcctata cttcatctcc cccttcgggc atgggctgcg gccagtggat    600
gtgggtttca tgaaggcatt gcatgagaag gtcaacatcg tgcctctcat cgccaaagct    660
gactgtcttg tccccagtga gatccggaag ctgaaggagc ggatccggga ggagattgac    720
aagtttggga tccatgtata ccagttccct gagtgtgact cggacgagga tgaggacttc    780
aagcagcagg accgggaact gaaggagagc gcgcccttcg ccgttatagg cagcaacacg    840
gtggtggagg ccaaggggca gcgggtccgg ggccgactgt acccctgggg gatcgtggag    900
gtggagaacc aggcgcattg cgacttcgtg aagctgcgca acatgctcat ccgcacgcat    960
atgcacgacc tcaaggacgt gacgtgcgac gtgcactacg agaactaccg cgcgcactgc   1020
atccagcaga tgaccagcaa actgacccag gacagccgca tggagagccc catccccgatc   1080
ctgccgctgc ccaccccgga cgccgagact gagaagctta tcaggatgaa ggatgaggaa   1140
```

```
ctgaggcgca tgcaggagat gctgcagagg atgaagcagc agatgcagga ccagtgacgc   1200
tcgccgcgga cacaccgtcc gtctccggga cgccctcgca cccctggaca ccagaccgga   1260
ctgttcccga cccggagacg cggggccaca gcccccagct gaccctaatt tattctcagc   1320
accacccct cccaggtcat tgtgtctgtt tccgaggggc ctggaccgta gccccgccc    1380
agctggccct ctctgacctt gggggatcag gagcgaagtt gggcgggact tcagagatcc   1440
gcctcccttg cccttccccc gcccccggac ggtcacagca cccaaaccgc aggccctgct   1500
ctggcaggca ggcaaagcta ggcagaagag gattcccagg atcctgggtc tgttccctgc   1560
cccagtgctg cagaacggac ttgggagccc tcctttgcct gctcccgcgg gtcacccagc   1620
gagtgctgag accccatttt ctgtcgaggc gggccgagtc ttcccttatc cccagacgcc   1680
tagcgggcag ggttgggctg aatcaaatgg gagccctcca gacataagga ggccagaggc   1740
tgcaaggagc ggggtcgtga ccgcttacac cccttctcca cagcccggcc cgacctggag   1800
ggcccccggg gcactgggcg gtgagccacc tcctggcaac tctcggtgcc gtcccctgcc   1860
ctcgctcgag gcctcttctc cccagcaccg ctgtggtgtg ccgggatcct gagcctaggc   1920
ctcccgatgt tcccacccgc atgatccctt cccgccacac gatgctccgt ttcttccgt    1980
tgtgaatgcc gcgtcctgtc ctggtgacag gagaacaatg ttggtgaacg tc           2032
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<210> 275
<211> 369
<212> PRT
<213> Homo sapiens

<400> 275

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Met Ser Thr Gly Leu Arg Tyr Lys Ser Lys Leu Ala Thr Pro Glu Asp
1               5                   10                  15
Lys Gln Asp Ile Asp Lys Gln Tyr Val Gly Phe Ala Thr Leu Pro Asn
            20                  25                  30
Gln Val His Arg Lys Ser Val Lys Lys Gly Phe Asp Phe Thr Leu Met
        35                  40                  45
Val Ala Gly Glu Ser Gly Leu Gly Lys Ser Thr Leu Val His Ser Leu
    50                  55                  60
Phe Leu Thr Asp Leu Tyr Lys Asp Arg Lys Leu Leu Ser Ala Glu Glu
65                  70                  75                  80
Arg Ile Ser Gln Thr Val Glu Ile Leu Lys His Thr Val Asp Ile Glu
                85                  90                  95
Glu Lys Gly Val Lys Leu Lys Leu Thr Ile Val Asp Thr Pro Gly Phe
            100                 105                 110
Gly Asp Ala Val Asn Asn Thr Glu Cys Trp Lys Pro Ile Thr Asp Tyr
        115                 120                 125
Val Asp Gln Gln Phe Glu Gln Tyr Phe Arg Asp Glu Ser Gly Leu Asn
    130                 135                 140
Arg Lys Asn Ile Gln Asp Asn Arg Val His Cys Cys Leu Tyr Phe Ile
145                 150                 155                 160
Ser Pro Phe Gly His Gly Leu Arg Pro Val Asp Val Gly Phe Met Lys
                165                 170                 175
Ala Leu His Glu Lys Val Asn Ile Val Pro Leu Ile Ala Lys Ala Asp
            180                 185                 190
Cys Leu Val Pro Ser Glu Ile Arg Lys Leu Lys Glu Arg Ile Arg Glu
        195                 200                 205
Glu Ile Asp Lys Phe Gly Ile His Val Tyr Gln Phe Pro Glu Cys Asp
    210                 215                 220
Ser Asp Glu Asp Glu Asp Phe Lys Gln Gln Asp Arg Glu Leu Lys Glu
225                 230                 235                 240
Ser Ala Pro Phe Ala Val Ile Gly Ser Asn Thr Val Val Glu Ala Lys
                245                 250                 255
Gly Gln Arg Val Arg Gly Arg Leu Tyr Pro Trp Gly Ile Val Glu Val
            260                 265                 270
Glu Asn Gln Ala His Cys Asp Phe Val Lys Leu Arg Asn Met Leu Ile
        275                 280                 285
Arg Thr His Met His Asp Leu Lys Asp Val Thr Cys Asp Val His Tyr
    290                 295                 300
Glu Asn Tyr Arg Ala His Cys Ile Gln Gln Met Thr Ser Lys Leu Thr
```

```
305                 310                 315                 320
Gln Asp Ser Arg Met Glu Ser Pro Ile Pro Ile Leu Pro Leu Pro Thr
                325                 330                 335
Pro Asp Ala Glu Thr Glu Lys Leu Ile Arg Met Lys Asp Glu Glu Leu
            340                 345                 350
Arg Arg Met Gln Glu Met Leu Gln Arg Met Lys Gln Gln Met Gln Asp
        355                 360                 365
Gln
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<210> 276
<211> 1344
<212> DNA
<213> Homo sapiens

<400> 276

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tgcagactga tatggattca ccactgctaa cacctcctgg ttggaactac aggaatagaa      60
ctggaaaggg aaaaaaggca gcattcacca catcccaatc ctgaatccaa gagtctaaga     120
tagtccccca ctcctatctc aggcttagag gattagatta atctcctgga gggaagactc     180
ttccttgaaa catttttttt tatctgcctg tagctattgg gataattcgg gaaatccaca     240
gggacagttc aagtcatctt tgtcctctac tttctgttgc actctcagcc ttgttctctt     300
tttagaaact gcatggtaac tattatatag ctaaagaaga gcattctgac ctctgccctg     360
ggacttcctg gatcctcctc ttcttataaa tacaagggca gagctggtat cccggggagc     420
caggaagcag tgagcccagg agtcctcggc cagccctgcc tgcccaccag gaggatgaag     480
gtctccgtgg ctgccctctc ctgcctcatg cttgttgctg tccttggatc ccaggcccag     540
ttcacaaatg atgcagagac agagttaatg atgtcaaagc ttccactgga aaatccagta     600
gttctgaaca gctttcactt tgctgctgac tgctgcacct cctacatctc acaaagcatc     660
ccgtgttcac tcatgaaaag ttattttgaa acgagcagcg agtgctccaa gccaggtgtc     720
atattcctca ccaagaaggg gcggcaagtc tgtgccaaac ccagtggtcc gggagttcag     780
gattgcatga aaaagctgaa gccctactca atataataat aaagagacaa aagaggccag     840
ccacccacct ccaacacctc ctgagcctct gaagctccca ccaggccagc tctcctccca     900
caacagcttc ccacagcatg aagatctccg tggctgccat tcccttcttc ctcctcatca     960
ccatcgccct agggaccaag actgaatcct cctcacgggg accttaccac ccctcagagt    1020
gctgcttcac ctacactacc tacaagatcc cgcgtcagcg gattatggat tactatgaga    1080
ccaacagcca gtgctccaag cccggaattg tcttcatcac caaaaggggc cattccgtct    1140
gtaccaaccc cagtgacaag tgggtccagg actatatcaa ggacatgaag gagaactgag    1200
tgacccagaa ggggtggcga aggcacagct cagagacata aagagaagat gccaaggccc    1260
cctcctccac ccaccgctaa ctctcagccc cagtcaccct cttggagctt ccctgctttg    1320
aattaaagac cactcatgct cttc                                          1344
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<210> 277
<211> 93
<212> PRT
<213> Homo sapiens

<400> 277

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Met Lys Ile Ser Val Ala Ala Ile Pro Phe Phe Leu Leu Ile Thr Ile
1               5                   10                  15
Ala Leu Gly Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro
            20                  25                  30
Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
        35                  40                  45
Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
    50                  55                  60
Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
65                  70                  75                  80
Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
                85                  90
```

<210> 278
<211> 1344

<212> DNA
<213> Homo sapiens

<400> 278
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tgcagactga tatggattca ccactgctaa cacctcctgg ttggaactac aggaatagaa      60
ctggaaaggg aaaaaaggca gcattcacca catcccaatc ctgaatccaa gagtctaaga     120
tagtccccca ctcctatctc aggcttagag gattagatta atctcctgga gggaagactc     180
ttccttgaaa catttttttt tatctgcctg tagctattgg gataattcgg gaaatccaca     240
gggacagttc aagtcatctt tgtcctctac tttctgttgc actctcagcc ttgttctctt     300
tttagaaact gcatggtaac tattatatag ctaaagaaga gcattctgac ctctgccctg     360
ggacttcctg gatcctcctc ttcttataaa tacaagggca gagctggtat cccggggagc     420
caggaagcag tgagcccagg agtcctcggc cagccctgcc tgcccaccag gaggatgaag     480
gtctccgtgg ctgccctctc ctgcctcatg cttgttgctg tccttggatc ccaggcccag     540
ttcacaaatg atgcagagac agagttaatg atgtcaaagc ttccactgga aaatccagta     600
gttctgaaca gctttcactt tgctgctgac tgctgcacct cctacatctc acaaagcatc     660
ccgtgttcac tcatgaaaag ttattttgaa acgagcagcg agtgctccaa gccaggtgtc     720
atattcctca ccaagaaggg gcggcaagtc tgtgccaaac ccagtggtcc gggagttcag     780
gattgcatga aaaagctgaa gccctactca atataataat aaagagacaa aagaggccag     840
ccacccacct ccaacacctc ctgagcctct gaagctccca ccaggccagc tctcctccca     900
caacagcttc ccacagcatg aagatctccg tggctgccat tcccttcttc ctcctcatca     960
ccatcgccct agggaccaag actgaatcct cctcacgggg accttaccac ccctcagagt    1020
gctgcttcac ctacactacc tacaagatcc cgcgtcagcg gattatggat tactatgaga    1080
ccaacagcca gtgctccaag cccggaattg tcttcatcac caaaagggc cattccgtct     1140
gtaccaaccc cagtgacaag tgggtccagg actatatcaa ggacatgaag gagaactgag    1200
tgacccagaa ggggtggcga aggcacagct cagagacata aagagaagat gccaaggccc    1260
cctcctccac ccaccgctaa ctctcagccc cagtcaccct cttggagctt ccctgctttg    1320
aattaaagac cactcatgct cttc                                           1344
```

<210> 279
<211> 93
<212> PRT
<213> Homo sapiens

<400> 279
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Met Lys Ile Ser Val Ala Ala Ile Pro Phe Phe Leu Leu Ile Thr Ile
1               5                   10                  15
Ala Leu Gly Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro
            20                  25                  30
Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
        35                  40                  45
Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
    50                  55                  60
Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
65                  70                  75                  80
Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
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<210> 280
<211> 1344
<212> DNA
<213> Homo sapiens

<400> 280
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ctggaaaggg aaaaaaggca gcattcacca catcccaatc ctgaatccaa gagtctaaga     120
tagtccccca ctcctatctc aggcttagag gattagatta atctcctgga gggaagactc     180
ttccttgaaa catttttttt tatctgcctg tagctattgg gataattcgg gaaatccaca     240
gggacagttc aagtcatctt tgtcctctac tttctgttgc actctcagcc ttgttctctt     300
tttagaaact gcatggtaac tattatatag ctaaagaaga gcattctgac ctctgccctg     360
ggacttcctg gatcctcctc ttcttataaa tacaagggca gagctggtat cccggggagc     420
caggaagcag tgagcccagg agtcctcggc cagccctgcc tgcccaccag gaggatgaag     480
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gtctccgtgg ctgccctctc ctgcctcatg cttgttgctg tccttggatc ccaggcccag 540
ttcacaaatg atgcagagac agagttaatg atgtcaaagc ttccactgga aaatccagta 600
gttctgaaca gctttcactt tgctgctgac tgctgcacct cctacatctc acaaagcatc 660
ccgtgttcac tcatgaaaag ttattttgaa acgagcagcg agtgctccaa gccaggtgtc 720
atattcctca ccaagaaggg gcggcaagtc tgtgccaaac ccagtggtcc gggagttcag 780
gattgcatga aaaagctgaa gccctactca atataataat aaagagacaa aagaggccag 840
ccacccacct ccaacacctc ctgagcctct gaagctccca ccaggccagc tctcctccca 900
caacagcttc ccacagcatg aagatctccg tggctgccat tcccttcttc ctcctcatca 960
ccatcgccct agggaccaag actgaatcct cctcacgggg accttaccac ccctcagagt 1020
gctgcttcac ctacactacc tacaagatcc cgcgtcagcg gattatggat tactatgaga 1080
ccaacagcca gtgctccaag cccggaattg tcttcatcac caaaaggggc cattccgtct 1140
gtaccaaccc cagtgacaag tgggtccagg actatatcaa ggacatgaag gagaactgag 1200
tgacccagaa ggggtggcga aggcacagct cagagacata aagagaagat gccaaggccc 1260
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aattaaagac cactcatgct cttc 1344

<210> 281
<211> 93
<212> PRT
<213> Homo sapiens

<400> 281
Met Lys Ile Ser Val Ala Ala Ile Pro Phe Phe Leu Leu Ile Thr Ile
1   5   10   15
Ala Leu Gly Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro
            20   25   30
Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
        35   40   45
Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
    50   55   60
Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
65   70   75   80
Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
                85   90

<210> 282
<211> 2750
<212> DNA
<213> Homo sapiens

<400> 282
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atgcctgtaa tcccagctac tcgggaggct gaagcaggag agttgcttga acctgggagg 240
cgtagattgc agtgagccaa gatcatccca ctgcactcca gcctgggcga cagagtgaga 300
cacagtctca aacaaaacaa aacaaaaagg aatttagagt agcccatggg gtagctatgc 360
ttaccaacat ccagtgggat ccccgtggat tctccctacc cctttttaag aggattgttg 420
ctaccttcta gggctccgtt tacagggatc actgatttct cagtcacgaa gaacaaaatt 480
atccagcttt gcttggacct gaccactaca gtccagaagg attgctttgt agcggaaatg 540
gaggataaag ttttaactgt ggtcaaggtt ttaaatggca tctgtgacaa aacaatccga 600
tctaccacag atcctgtgat gagccagtgt gcatgtctgg aggaagttca cttaccaaac 660
attaaacctg ggaaggcct gggcatgtac atcaaatcaa cctatgatgg gttacacgtg 720
attactggaa ccacagaaaa ttctcctgca gacagatctc agaagattca tgctggtgac 780
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ttaaactgaa tgtatgatat tttgttagaa tggaaaagta ctatcttgtt aatttaagta 2700
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<210> 283
<211> 380
<212> PRT
<213> Homo sapiens

<220>
<221> VARIANT
<222> (1)...(380)
<223> Xaa = Any Amino Acid

<400> 283
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20 25 30
Cys Leu Glu Glu Val His Leu Pro Asn Ile Lys Pro Gly Glu Gly Leu
35 40 45
Gly Met Tyr Ile Lys Ser Thr Tyr Asp Gly Leu His Val Ile Thr Gly
50 55 60
Thr Thr Glu Asn Ser Pro Ala Asp Arg Ser Gln Lys Ile His Ala Gly
65 70 75 80
Asp Glu Val Ile Gln Val Asn Gln Gln Thr Val Val Gly Trp Gln Leu
85 90 95
Lys Asn Leu Val Lys Lys Leu Arg Glu Asn Pro Thr Gly Val Val Leu
100 105 110
Leu Leu Lys Lys Arg Pro Thr Gly Ser Phe Asn Phe Thr Pro Ala Pro
115 120 125
Leu Lys Asn Leu Arg Trp Lys Pro Pro Leu Val Gln Thr Ser Pro Pro
130 135 140
Pro Ala Thr Thr Gln Ser Pro Glu Ser Thr Met Asp Thr Ser Leu Lys
145 150 155 160
Lys Glu Lys Ser Ala Ile Leu Asp Leu Tyr Ile Pro Pro Pro Pro Ala
165 170 175
Val Pro Tyr Ser Pro Arg Asp Glu Asn Gly Ser Phe Val Tyr Gly Gly

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                180                           185                           190
Ser Ser Lys Cys Lys Gln Pro Leu Pro Gly Pro Lys Gly Ser Glu Ser
        195                           200                           205
Pro Asn Ser Phe Leu Asp Gln Glu Ser Arg Arg Arg Arg Phe Thr Ile
    210                           215                           220
Ala Asp Ser Asp Gln Leu Pro Gly Tyr Ser Val Glu Thr Asn Ile Leu
225                           230                           235                           240
Pro Thr Lys Met Arg Glu Lys Thr Pro Ser Tyr Xaa Lys Pro Arg Pro
                    245                           250                           255
Leu Ser Met Pro Ala Asp Gly Asn Trp Met Gly Ile Val Asp Pro Phe
                260                           265                           270
Ala Arg Pro Arg Gly His Gly Arg Lys Gly Glu Asp Ala Leu Cys Arg
        275                           280                           285
Tyr Phe Ser Asn Glu Arg Ile Pro Pro Ile Ile Glu Glu Ser Ser Ser
    290                           295                           300
Pro Pro Tyr Arg Phe Ser Arg Pro Thr Thr Glu Arg His Leu Val Arg
305                           310                           315                           320
Gly Ala Asp Tyr Ile Arg Gly Ser Arg Cys Tyr Ile Asn Ser Asp Leu
                    325                           330                           335
His Ser Ser Ala Thr Ile Pro Phe Gln Glu Glu Gly Thr Lys Lys Lys
                340                           345                           350
Ser Gly Ser Ser Ala Thr Lys Ser Ser Ser Thr Glu Pro Ser Leu Leu
        355                           360                           365
Val Ser Trp Phe Thr Arg Leu Lys Leu Leu Thr His
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<210> 284
<211> 1789
<212> DNA
<213> Homo sapiens

<400> 284

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tcctcattgg ctgatggatc ccaaggggct cctctccttg accttcgtgc tgtttctctc     180
cctggctttt ggggcaagct acggaacagg tggcgcatg atgaactgcc caaagattct      240
ccggcagttg ggaagcaaag tgctgctgcc cctgacatat gaaaggataa ataagagcat     300
gaacaaaagc atccacattg tcgtcacaat ggcaaaatca ctggagaaca gtgtcgagaa     360
caaaatagtg tctcttgatc catccgaagc aggccctcca cgttatctag gagatcgcta     420
caagttttat ctggagaatc tcaccctggg gatacgggaa agcaggaagg aggatgaggg     480
atggtacctt atgaccctgg agaaaaatgt ttcagttcag cgcttttgcc tgcagttgag     540
gctttatgag caggtctcca ctccagaaat taaagtttta aacaagaccc aggagaacgg     600
gacctgcacc ttgatactgg gctgcacagt ggagaagggg gaccatgtgg cttacagctg     660
gagtgaaaag gcgggcaccc acccactgaa cccagccaac agctcccacc tcctgtccct     720
caccctcggc ccccagcatg ctgacaatat ctacatctgc accgtgagca accctatcag     780
caacaattcc cagaccttca gcccgtggcc cggatgcagg acagacccct cagaaacaaa     840
accatgggca gtgtatgctg ggctgttagg gggtgtcatc atgattctca tcatggtggt     900
aatactacag ttgagaagaa gaggtaaaac gaaccattac cagacaacag tggaaaaaaa     960
aagccttacg atctatgccc aagtccagaa accaggtcct cttcagaaga aacttgactc    1020
cttcccagct caggaccctt gcaccaccat atatgttgct gccacagagc ctgtcccaga    1080
gtctgtccag gaaacaaatt ccatcacagt ctatgctagt gtgacacttc cagagagctg    1140
acaccagaga ccaacaaagg gactttctga aggaaaatgg aaaaaccaaa atgaacactg    1200
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gatcaactcc ctggtgatgt ttcttccaca tacatctgtg aaatgaacaa ggaagtgagg    1320
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taacagcgtt ccatctttgt gttgtagcag atgaaatgga cagtaatgtg agttcagact    1440
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tgagtaccta tctcacacac tgaccaccag tcacaaagtc tggaaaagtt tacattttgg    1560
ctatctttac tttgttctgg gagctgatca tgataacctg cagacctgat caagcctctg    1620
tgcctcagtt tctctctcag gataaagagt gaatagaggc cgaagggtga atttcttatt    1680
atacataaaa cactctgata ttattgtata aaggaagcta agaatattat tttatttgca    1740
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<210> 285
<211> 335
<212> PRT
<213> Homo sapiens

<400> 285
Met Asp Pro Lys Gly Leu Leu Ser Leu Thr Phe Val Leu Phe Leu Ser
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Leu Ala Phe Gly Ala Ser Tyr Gly Thr Gly Gly Arg Met Met Asn Cys
20 25 30
Pro Lys Ile Leu Arg Gln Leu Gly Ser Lys Val Leu Leu Pro Leu Thr
35 40 45
Tyr Glu Arg Ile Asn Lys Ser Met Asn Lys Ser Ile His Ile Val Val
50 55 60
Thr Met Ala Lys Ser Leu Glu Asn Ser Val Glu Asn Lys Ile Val Ser
65 70 75 80
Leu Asp Pro Ser Glu Ala Gly Pro Pro Arg Tyr Leu Gly Asp Arg Tyr
85 90 95
Lys Phe Tyr Leu Glu Asn Leu Thr Leu Gly Ile Arg Glu Ser Arg Lys
100 105 110
Glu Asp Glu Gly Trp Tyr Leu Met Thr Leu Glu Lys Asn Val Ser Val
115 120 125
Gln Arg Phe Cys Leu Gln Leu Arg Leu Tyr Glu Gln Val Ser Thr Pro
130 135 140
Glu Ile Lys Val Leu Asn Lys Thr Gln Glu Asn Gly Thr Cys Thr Leu
145 150 155 160
Ile Leu Gly Cys Thr Val Glu Lys Gly Asp His Val Ala Tyr Ser Trp
165 170 175
Ser Glu Lys Ala Gly Thr His Pro Leu Asn Pro Ala Asn Ser Ser His
180 185 190
Leu Leu Ser Leu Thr Leu Gly Pro Gln His Ala Asp Asn Ile Tyr Ile
195 200 205
Cys Thr Val Ser Asn Pro Ile Ser Asn Asn Ser Gln Thr Phe Ser Pro
210 215 220
Trp Pro Gly Cys Arg Thr Asp Pro Ser Glu Thr Lys Pro Trp Ala Val
225 230 235 240
Tyr Ala Gly Leu Leu Gly Gly Val Ile Met Ile Leu Ile Met Val Val
245 250 255
Ile Leu Gln Leu Arg Arg Arg Gly Lys Thr Asn His Tyr Gln Thr Thr
260 265 270
Val Glu Lys Lys Ser Leu Thr Ile Tyr Ala Gln Val Gln Lys Pro Gly
275 280 285
Pro Leu Gln Lys Lys Leu Asp Ser Phe Pro Ala Gln Asp Pro Cys Thr
290 295 300
Thr Ile Tyr Val Ala Ala Thr Glu Pro Val Pro Glu Ser Val Gln Glu
305 310 315 320
Thr Asn Ser Ile Thr Val Tyr Ala Ser Val Thr Leu Pro Glu Ser
325 330 335

<210> 286
<211> 305
<212> PRT
<213> Homo sapiens

<400> 286
Met Asp Pro Lys Gly Leu Leu Ser Leu Thr Phe Val Leu Phe Leu Ser
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Leu Ala Phe Gly Ala Ser Tyr Gly Thr Gly Gly Arg Met Met Asn Cys
20 25 30

Pro Lys Ile Leu Arg Gln Leu Gly Ser Lys Val Leu Leu Pro Leu Thr
35 40 45
Tyr Glu Arg Ile Asn Lys Ser Met Asn Lys Ser Ile His Ile Val Val
50 55 60
Thr Met Ala Lys Ser Leu Glu Asn Ser Val Glu Asn Lys Ile Val Ser
65 70 75 80
Leu Asp Pro Ser Glu Ala Gly Pro Pro Arg Tyr Leu Gly Asp Arg Tyr
85 90 95
Lys Phe Tyr Leu Glu Asn Leu Thr Leu Gly Ile Arg Glu Ser Arg Lys
100 105 110
Glu Asp Glu Gly Trp Tyr Leu Met Thr Leu Glu Lys Asn Val Ser Val
115 120 125
Gln Arg Phe Cys Leu Gln Leu Arg Leu Tyr Glu Gln Val Ser Thr Pro
130 135 140
Glu Ile Lys Val Leu Asn Lys Thr Gln Glu Asn Gly Thr Cys Thr Leu
145 150 155 160
Ile Leu Gly Cys Thr Val Glu Lys Gly Asp His Val Ala Tyr Ser Trp
165 170 175
Ser Glu Lys Ala Gly Thr His Pro Leu Asn Pro Ala Asn Ser Ser His
180 185 190
Leu Leu Ser Leu Thr Leu Gly Pro Gln His Ala Asp Asn Ile Tyr Ile
195 200 205
Cys Thr Val Ser Asn Pro Ile Ser Asn Asn Ser Gln Thr Phe Ser Pro
210 215 220
Trp Pro Gly Cys Arg Thr Asp Pro Ser Gly Lys Thr Asn His Tyr Gln
225 230 235 240
Thr Thr Val Glu Lys Lys Ser Leu Thr Ile Tyr Ala Gln Val Gln Lys
245 250 255
Pro Gly Pro Leu Gln Lys Lys Leu Asp Ser Phe Pro Ala Gln Asp Pro
260 265 270
Cys Thr Thr Ile Tyr Val Ala Ala Thr Glu Pro Val Pro Glu Ser Val
275 280 285
Gln Glu Thr Asn Ser Ile Thr Val Tyr Ala Ser Val Thr Leu Pro Glu
290 295 300
Ser
305

<210> 287
<211> 298
<212> PRT
<213> Homo sapiens

<400> 287
Met Asp Pro Lys Gly Leu Leu Ser Leu Thr Phe Val Leu Phe Leu Ser
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Leu Ala Phe Gly Ala Ser Tyr Gly Thr Gly Gly Arg Met Met Asn Cys
20 25 30
Pro Lys Ile Leu Arg Gln Leu Gly Ser Lys Val Leu Leu Pro Leu Thr
35 40 45
Tyr Glu Arg Ile Asn Lys Ser Met Asn Lys Ser Ile His Ile Val Val
50 55 60
Thr Met Ala Lys Ser Leu Glu Asn Ser Val Glu Asn Lys Ile Val Ser
65 70 75 80
Leu Asp Pro Ser Glu Ala Gly Pro Pro Arg Tyr Leu Gly Asp Arg Tyr
85 90 95
Lys Phe Tyr Leu Glu Asn Leu Thr Leu Gly Ile Arg Glu Ser Arg Lys
100 105 110
Glu Asp Glu Gly Trp Tyr Leu Met Thr Leu Glu Lys Asn Val Ser Val
115 120 125
Gln Arg Phe Cys Leu Gln Leu Arg Leu Tyr Glu Gln Val Ser Thr Pro
130 135 140

Glu Ile Lys Val Leu Asn Lys Thr Gln Glu Asn Gly Thr Cys Thr Leu
145 150 155 160
Ile Leu Gly Cys Thr Val Glu Lys Gly Asp His Val Ala Tyr Ser Trp
165 170 175
Ser Glu Lys Ala Gly Thr His Pro Leu Asn Pro Ala Asn Ser Ser His
180 185 190
Leu Leu Ser Leu Thr Leu Gly Pro Gln His Ala Asp Asn Ile Tyr Ile
195 200 205
Cys Thr Val Ser Asn Pro Ile Ser Asn Asn Ser Gln Thr Phe Ser Pro
210 215 220
Trp Pro Gly Cys Arg Thr Asp Pro Ser Glu Thr Lys Pro Trp Ala Val
225 230 235 240
Tyr Ala Gly Leu Leu Gly Gly Val Ile Met Ile Leu Ile Met Val Val
245 250 255
Ile Leu Gln Leu Arg Arg Arg Gly Lys Thr Asn His Tyr Gln Thr Thr
260 265 270
Val Glu Lys Lys Ser Leu Thr Ile Tyr Ala Gln Val Gln Lys Pro Gly
275 280 285
Asp Thr His His Gln Thr Ser Asp Leu Phe
290 295

<210> 288
<211> 3640
<212> DNA
<213> Homo sapiens

<400> 288
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cagacattag gaaatgccaa ggcattctgt ggaatgaaat attcatatgt gctaaaaata 2040

aagattttat cagctcatga taaaggtact catgttgagg tcaatgtgaa gattaaaaag 2100
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Ser Glu Asn Thr Asp Leu Thr Cys Arg Gln Pro Lys Cys Asp Lys Cys
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Ser Ser Phe Arg Phe Pro Arg Thr Trp Trp Gln Ser Ala Glu Asp Val
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His Arg Glu Lys Ile Gln Leu Asp Leu Glu Ala Glu Phe Tyr Phe Thr
115 120 125
His Leu Ile Val Met Phe Lys Ser Pro Arg Pro Ala Ala Met Val Leu
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Asp Arg Ser Gln Asp Phe Gly Lys Thr Trp Lys Pro Tyr Lys Tyr Phe
145 150 155 160
Ala Thr Asn Cys Ser Ala Thr Phe Gly Leu Glu Asp Asp Val Val Lys
165 170 175
Lys Gly Ala Ile Cys Thr Ser Lys Tyr Ser Ser Pro Phe Pro Cys Thr
180 185 190
Gly Gly Glu Val Ile Phe Lys Ala Leu Ser Pro Pro Tyr Asp Thr Glu
195 200 205
Asn Pro Tyr Ser Ala Lys Val Gln Glu Gln Leu Lys Ile Thr Asn Leu

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225 230 235 240
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Ile Val Lys Gly Ser Cys Phe Cys Asn Gly His Ala Asp Gln Cys Ile
260 265 270
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275 280 285
Val His Gly Lys Cys Met Cys Lys His Asn Thr Ala Gly Ser His Cys
290 295 300
Gln His Cys Ala Pro Leu Tyr Asn Asp Arg Pro Trp Glu Ala Ala Asp
305 310 315 320
Gly Lys Thr Gly Ala Pro Asn Glu Cys Arg Thr Cys Lys Cys Asn Gly
325 330 335
His Ala Asp Thr Cys His Phe Asp Val Asn Val Trp Glu Ala Ser Gly
340 345 350
Asn Arg Ser Gly Gly Val Cys Asp Asp Cys Gln His Asn Thr Glu Gly
355 360 365
Gln Tyr Cys Gln Arg Cys Lys Pro Gly Phe Tyr Arg Asp Leu Arg Arg
370 375 380
Pro Phe Ser Ala Pro Asp Ala Cys Lys Pro Cys Ser Cys His Pro Val
385 390 395 400
Gly Ser Ala Val Leu Pro Ala Asn Ser Val Thr Phe Cys Asp Pro Ser
405 410 415
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420 425 430
Arg Cys Met Val Gly Tyr Trp Gly Phe Gly Asp Tyr Gly Cys Arg Pro
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Cys Asp Cys Ala Gly Ser Cys Asp Pro Ile Thr Gly Asp Cys Ile Ser
450 455 460
Ser His Thr Asp Ile Asp Trp Tyr His Glu Val Pro Asp Phe Arg Pro
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485 490 495
Phe Ser Ala Leu Leu His Ser Gly Lys Cys Glu Cys Lys Glu Gln Thr
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Lys Ile Lys Ile Leu Ser Ala His Asp Lys Gly Thr His Val Glu Val
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Arg Gly Lys Arg Thr Leu Tyr Pro Glu Ser Trp Thr Asp Arg Gly Cys
565 570 575
Thr Cys Pro Ile Leu Asn Pro Gly Leu Glu Tyr Leu Val Ala Gly His
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Glu Asp Ile Arg Thr Gly Lys Leu Ile Val Asn Met Lys Ser Phe Val
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Arg Glu Cys Lys
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<213> Mouse

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<212> PRT
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35 40 45
Arg Ala Cys Arg Glu Leu Gly Gly Asn Leu Ala Thr Pro Arg Thr Pro
50 55 60
Glu Glu Ala Gln Arg Val Asp Ser Leu Val Gly Val Gly Pro Ala Asn
65 70 75 80
Gly Leu Leu Trp Ile Gly Leu Gln Arg Gln Ala Arg Gln Cys Gln Pro
85 90 95

Gln Arg Pro Leu Arg Gly Phe Ile Trp Thr Thr Gly Asp Gln Asp Thr
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Ala Phe Thr Asn Trp Ala Gln Pro Ala Thr Glu Gly Pro Cys Pro Ala
115 120 125
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130 135 140
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145 150 155 160
Glu Gly Ala Cys Pro Ala Leu Pro Leu Glu Val Gly Gln Ala Gly Pro
165 170 175
Ala Val Tyr Thr Thr Pro Phe Asn Leu Val Ser Ser Glu Phe Glu Trp
180 185 190
Leu Pro Phe Gly Ser Val Ala Ala Val Gln Cys Gln Ala Gly Arg Gly
195 200 205
Ala Ser Leu Leu Cys Val Lys Gln Pro Ser Gly Gly Val Gly Trp Ser
210 215 220
Gln Thr Gly Pro Leu Cys Pro Gly Thr Gly Cys Gly Pro Asp Asn Gly
225 230 235 240
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245 250 255
Arg Cys Ser Glu Gly Phe Arg Leu Ala Ala Asp Gly His Ser Cys Glu
260 265 270
Asp Pro Cys Ala Gln Ala Pro Cys Glu Gln Gln Cys Glu Pro Gly Gly
275 280 285
Pro Gln Gly Tyr Ser Cys His Cys Arg Leu Gly Phe Arg Pro Ala Glu
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305 310 315 320
Val Cys Gln Gln Met Cys Val Asn Tyr Val Gly Gly Phe Glu Cys Tyr
325 330 335
Cys Ser Glu Gly His Glu Leu Glu Ala Asp Gly Ile Ser Cys Ser Pro
340 345 350
Ala Gly Ala Met Gly Ala Gln Ala Ser Gln Asp Leu Arg Asp Glu Leu
355 360 365
Leu Asp Asp Gly Glu Glu Gly Glu Asp Glu Glu Glu Pro Trp Glu Asp
370 375 380
Phe Asp Gly Thr Trp Thr Glu Glu Gln Gly Ile Leu Trp Leu Ala Pro
385 390 395 400
Thr His Pro Pro Asp Phe Gly Leu Pro Tyr Arg Pro Asn Phe Pro Gln
405 410 415
Asp Gly Glu Pro Gln Arg Leu His Leu Glu Pro Thr Trp Pro Pro Pro
420 425 430
Leu Ser Ala Pro Arg Gly Pro Tyr His Ser Ser Val Val Ser Ala Thr
435 440 445
Arg Pro Met Val Ile Ser Ala Thr Arg Pro Thr Leu Pro Ser Ala His
450 455 460
Lys Thr Ser Val Ile Ser Ala Thr Arg Pro Pro Leu Ser Pro Val His
465 470 475 480
Pro Pro Ala Met Ala Pro Ala Thr Pro Pro Ala Val Phe Ser Glu His
485 490 495
Gln Ile Pro Lys Ile Lys Ala Asn Tyr Pro Asp Leu Pro Phe Gly His
500 505 510
Lys Pro Gly Ile Thr Ser Ala Thr His Pro Ala Arg Ser Pro Pro Tyr
515 520 525
Gln Pro Pro Ile Ile Ser Thr Asn Tyr Pro Gln Val Phe Pro Pro His
530 535 540
Gln Ala Pro Met Ser Pro Asp Thr His Thr Ile Thr Tyr Leu Pro Pro
545 550 555 560
Val Pro Pro His Leu Asp Pro Gly Asp Thr Thr Ser Lys Ala His Gln
565 570 575
His Pro Leu Leu Pro Asp Ala Pro Gly Ile Arg Thr Gln Ala Pro Gln

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    610                 615                 620
Pro Ser Ser Pro Leu Pro Pro Gln Arg Pro Thr Asn Gln Thr Ser Ser
625                 630                 635                 640
Ile Ser Pro Thr His Ser Tyr Ser Arg Ala Pro Leu Val Pro Arg Glu
                645                 650                 655
Gly Val Pro Ser Pro Lys Ser Val Pro Gln Leu Pro Ser Val Pro Ser
            660                 665                 670
Thr Ala Ala Pro Thr Ala Leu Ala Glu Ser Gly Leu Ala Gly Gln Ser
        675                 680                 685
Gln Arg Asp Asp Arg Trp Leu Leu Val Ala Leu Leu Val Pro Thr Cys
    690                 695                 700
Val Phe Leu Val Val Leu Leu Ala Leu Gly Ile Val Tyr Cys Thr Arg
705                 710                 715                 720
Cys Gly Ser His Ala Pro Asn Lys Arg Ile Thr Asp Cys Tyr Arg Trp
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<213> Mouse

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35 40 45
Thr Pro Thr Ile Glu Asp Phe His Arg Lys Val Tyr Asn Ile His Gly
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Asp Met Tyr Gln Leu Asp Ile Leu Asp Thr Ser Gly Asn His Pro Phe
65 70 75 80
Pro Ala Met Arg Arg Leu Ser Ile Leu Thr Gly Asp Val Phe Ile Leu
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Val Phe Ser Leu Asp Ser Arg Glu Ser Phe Asp Glu Val Lys Arg Leu
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Gln Lys Gln Ile Leu Glu Val Lys Ser Cys Leu Lys Asn Lys Thr Lys
115 120 125
Glu Ala Ala Glu Leu Pro Met Val Ile Cys Gly Asn Lys Asn Asp His
130 135 140
Ser Glu Leu Cys Arg Gln Val Pro Ala Met Glu Ala Glu Leu Leu Val
145 150 155 160
Ser Gly Asp Glu Asn Cys Ala Tyr Phe Glu Val Ser Ala Lys Lys Asn
165 170 175
Thr Asn Val Asn Glu Met Phe Tyr Val Leu Phe Ser Met Ala Lys Leu
180 185 190
Pro His Glu Met Ser Pro Ala Leu His His Lys Ile Ser Val Gln Tyr
195 200 205
Gly Asp Ala Phe His Pro Arg Pro Phe Cys Met Arg Arg Thr Lys Val
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Ala Gly Ala Tyr Gly Met Val Ser Pro Phe Ala Arg Arg Pro Ser Val
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Gly Gly Ala His Asn Pro Ala Arg Arg Arg Val Val Cys Gly Gly Gly
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Asp Leu Pro Glu Pro Pro Asp Pro Gly Leu Leu Pro Asn Gly Thr Ile
65                  70                  75                  80
Thr Leu Leu Leu Ser Asn Asn Lys Ile Thr Gly Leu Arg Asn Gly Ser
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Phe Leu Gly Leu Ser Leu Leu Glu Lys Leu Asp Leu Arg Ser Asn Val
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Phe Gln Gly Leu Pro Arg Leu Leu Arg Leu Asn Ile Ser Gly Asn Ile
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Tyr Ser Ser Leu Gln Pro Gly Val Phe Asp Glu Leu Pro Ala Leu Lys
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Ile Val Asp Phe Gly Thr Glu Phe Leu Thr Cys Asp Cys Arg Leu Arg
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Trp Leu Leu Pro Trp Ala Arg Asn His Ser Leu Gln Leu Ser Glu Arg
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Thr Leu Cys Ala Tyr Pro Ser Ala Leu His Ala His Ala Leu Ser Ser
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His Tyr Leu Ile Pro Ser Leu Arg Gln Val Val Phe Gln Gly Asp Arg
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His Trp Tyr His Asn Gly Ala Pro Met Glu Ser Asp Glu Gln Ala Gly
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Glu Leu Thr Leu Ser His Ile Gly Val Trp Ala Ser Gly Glu Trp Glu
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Cys Ser Val Ser Thr Val Gln Gly Asn Thr Ser Lys Lys Val Glu Ile
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Val Val Leu Glu Thr Ser Ala Ser Tyr Cys Pro Ala Glu Arg Val Thr
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675 680 685
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755 760 765
Ala Leu Leu Leu Leu Cys Leu Phe Ser Thr Ile Ile Thr Tyr Ile Leu
770 775 780
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785 790 795 800
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Pro Arg Glu Ser Pro Ala Gln Val Leu Lys Pro Gly Lys Thr Gln Leu
50 55 60
Ser Gln Asp Leu Gly Gly Gly Ser Leu Ala Ile Asp Thr Leu Pro Asp
65 70 75 80
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85 90 95
Val Tyr Gly Pro Gly Glu Lys Gln Ser Gln Asp Leu Trp Val Asp Leu
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Ala Val Ala Asn Arg Ser His Val Lys Ile His Arg Ile Leu Ser Ser
115 120 125
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130 135 140
Tyr Gly His Pro Leu Arg Gln Ile Thr Ile Ala Thr Gly Gly Phe Ile
145 150 155 160
Phe Met Gly Asp Met Leu His Arg Met Leu Thr Ala Thr Gln Tyr Val
165 170 175
Ala Pro Leu Met Ala Asn Phe Asn Pro Gly Tyr Ser Asp Asn Ser Thr
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Val Ala Tyr Phe Asp Asn Gly Thr Val Phe Val Val Gln Trp Asp His
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Val Tyr Leu Gln Asp Arg Glu Asp Arg Gly Ser Phe Thr Phe Gln Ala

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            260                 265                 270
Ser Gln Arg Arg Thr Ile Phe Glu Tyr His Arg Val Glu Leu Asp Ser
        275                 280                 285
Ser Lys Ile Thr Thr Thr Ser Ala Val Glu Phe Thr Pro Leu Pro Thr
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Cys Leu Gln His Gln Ser Cys Asp Thr Cys Val Ser Ser Asn Leu Thr
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385                 390                 395                 400
Asn Pro Tyr Ala Glu Gly Asp Gly Leu Pro Asp His Ser Ser Pro Lys
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Ser Lys Gly Pro Pro Val His Leu Gly Thr Ile Val Gly Ile Val Leu
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Ala Val Leu Leu Val Ala Ala Ile Ile Leu Ala Gly Ile Tyr Ile Ser
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Gly His Pro Asn Ser Asn Ala Ala Leu Phe Phe Ile Glu Arg Arg Pro
    450                 455                 460
His His Trp Pro Ala Met Lys Phe His Asn His Pro Asn His Ser Thr
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<213> Mouse

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Trp Asn Glu Glu Gly Val Glu Val Asp Ser Gln Ala Tyr Asn His Arg
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Trp Lys Arg Asn Val Asp Pro Phe Lys Ala Val Asp Thr Asn Arg Ala
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His Asn Tyr Tyr Ile Ser Arg Ile Tyr Gly Pro Ala Asp Ser Ala Ser
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Arg Asp Leu Trp Val Asn Ile Asp Gln Met Glu Lys Asp Lys Val Lys
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Ile His Gly Ile Leu Ser Asn Thr His Arg Gln Ala Ala Arg Val Asn
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Leu Ser Phe Asp Phe Pro Phe Tyr Gly His Phe Leu Asn Glu Val Thr
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Val Ala Thr Gly Gly Phe Ile Tyr Thr Gly Glu Val Val His Arg Met
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Ser Val Ser Arg Asn Ser Thr Val Arg Tyr Phe Asp Asn Gly Thr Ala
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Leu Val Val Gln Trp Asp His Val His Leu Gln Asp Asn Tyr Asn Leu
225                 230                 235                 240
Gly Ser Phe Thr Phe Gln Ala Thr Leu Leu Met Asp Gly Arg Ile Ile
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Phe Gly Tyr Lys Glu Ile Pro Val Leu Val Thr Gln Ile Ser Ser Thr
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Asn His Pro Val Lys Val Gly Leu Ser Asp Ala Phe Val Val Val His
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Arg Ile Gln Gln Ile Pro Asn Val Arg Arg Arg Thr Ile Tyr Glu Tyr
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Cys Val Ser Ser Gln Ile Gly Phe Asn Cys Ser Trp Cys Ser Lys Leu
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Gln Arg Cys Ser Ser Gly Phe Asp Arg His Arg Gln Asp Trp Val Asp
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Ser Gly Cys Pro Glu Glu Val Gln Ser Lys Glu Lys Met Cys Glu Lys
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Thr Glu Pro Gly Glu Thr Ser Gln Thr Thr Thr Thr Ser His Thr Thr
385                 390                 395                 400
Thr Met Gln Phe Arg Val Leu Thr Thr Thr Arg Arg Ala Val Thr Ser
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Gln Met Pro Thr Ser Leu Pro Thr Glu Asp Asp Thr Lys Ile Ala Leu
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Lys Gly Gly Thr Leu His Ala Gly Leu Ile Val Gly Ile Leu Ile Leu
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Val Leu Ile Ile Ala Ala Ala Ile Leu Val Thr Val Tyr Met Tyr His
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<211> 562
<212> PRT
<213> Mouse

<400> 301

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        35                  40                  45
Lys Ser Gly Ser Val Leu His His Trp Asn Glu Ile Tyr Tyr Phe Val
    50                  55                  60
Glu Gln Leu Ala His Arg Phe Ile Ser Pro Gln Leu Arg Met Ser Phe
65                  70                  75                  80
Ile Val Phe Ser Thr Arg Gly Thr Thr Leu Met Lys Leu Thr Glu Asp
                85                  90                  95
Arg Glu Gln Ile Arg Gln Gly Leu Glu Glu Leu Gln Lys Val Leu Pro
            100                 105                 110
Gly Gly Asp Thr Tyr Met His Glu Gly Phe Glu Arg Ala Ser Glu Gln
        115                 120                 125
Ile Tyr Tyr Glu Asn Ser Gln Gly Tyr Arg Thr Ala Ser Val Ile Ile
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Ala Leu Thr Asp Gly Glu Leu His Glu Asp Leu Phe Phe Tyr Ser Glu
145                 150                 155                 160
Arg Glu Ala Asn Arg Ser Arg Asp Leu Gly Ala Ile Val Tyr Cys Val
                165                 170                 175
Gly Val Lys Asp Phe Asn Glu Thr Gln Leu Ala Arg Ile Ala Asp Ser
            180                 185                 190
Lys Asp His Val Phe Pro Val Asn Asp Gly Phe Gln Ala Leu Gln Gly
        195                 200                 205
Ile Ile His Ser Ile Leu Lys Lys Ser Cys Ile Glu Ile Leu Ala Ala
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Glu Pro Ser Thr Ile Cys Ala Gly Glu Ser Phe Gln Val Val Val Arg
225                 230                 235                 240
Gly Asn Gly Phe Arg His Ala Arg Asn Val Asp Arg Val Leu Cys Ser
                245                 250                 255
Phe Lys Ile Asn Asp Ser Val Thr Leu Asn Glu Lys Pro Phe Ala Val
            260                 265                 270
Glu Asp Thr Tyr Leu Leu Cys Pro Ala Pro Ile Leu Lys Glu Val Gly
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Met Lys Ala Ala Leu Gln Val Ser Met Asn Asp Gly Leu Ser Phe Ile
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Ser Ser Ser Val Ile Ile Thr Thr Thr His Cys Ser Asp Gly Ser Ile
305                 310                 315                 320
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Leu Trp Trp Phe Trp Pro Leu Cys Cys Thr Val Ile Ile Lys Glu Val
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Pro Pro Pro Pro Val Glu Glu Ser Glu Glu Glu Asp Asp Asp Gly Leu
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Pro Lys Lys Lys Trp Pro Thr Val Asp Ala Ser Tyr Tyr Gly Gly Arg
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Ser Thr Glu Glu Gly Ala Lys Leu Glu Lys Ala Lys Asn Ala Arg Val
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Lys Met Pro Glu Gln Glu Tyr Glu Phe Pro Glu Pro Arg Asn Leu Asn
420 425 430
Asn Asn Met Arg Arg Pro Ser Ser Pro Arg Lys Trp Tyr Ser Pro Ile
435 440 445
Lys Gly Lys Leu Asp Ala Leu Trp Val Leu Leu Arg Lys Gly Tyr Asp
450 455 460
Arg Val Ser Val Met Arg Pro Gln Pro Gly Asp Thr Gly Arg Cys Ile
465 470 475 480
Asn Phe Thr Arg Val Lys Asn Ser Gln Pro Ala Lys Tyr Pro Leu Asn
485 490 495
Asn Thr Tyr His Pro Ser Ser Pro Pro Pro Ala Pro Ile Tyr Thr Pro
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Pro Pro Pro Ala Pro His Cys Pro Pro Pro Ala Pro Ser Ala Pro Thr
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<211> 2690
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<213> Mouse

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Ile Gln His Glu Phe Ser Leu Thr Arg Glu Lys Arg Lys His Val Leu
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Thr Lys Asp Glu Gly Asp Tyr Phe Cys Glu Leu Gln Val Ser Gly Ala
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PEM's
Complete web table #25 (PEM3) + #47 (PEM6) are G1, rest are G3

Table 1. Previously characterized and novel Pan Endothelial Markers. The most abundant tags derived by summing the tags from Normal EC (N-EC's) and Tumor EC (T-EC's) SAGE libraries are listed in descending order. N-EC and T-EC SAGE libraries contained 96,694 and 96,588 SAGE tags respectively. For comparison, the corresponding number of SAGE tags found in cultured human umbilical vein endothelial cells (HUVEC), human dermal microvascular endothelial cells (HMVEC), and non-endothelial cell lines (Cell Lines) are shown. The HUVEC SAGE library contained 290,000 tags and the HMVEC library 111,000 tags. Non-endothelial cell lines consisted of $1.8x10^6$ tags derived from a total of 14 different cancer cell lines including colon, breast, lung, and pancreatic cancers, as well as one non-transformed keratinocyte cell line, two kidney epithelial cell lines, and normal monocytes. Tag numbers for each group were normalized to 100,000 transcripts. A 'Description' of the gene product corresponding to each tag is given, followed by alternative names in parenthesis. The sequence CATG precedes all tags and the 15th base (11th shown) was determined as previously described by Velculescu et. al. (Nat Genet 1999 Dec;23(4):387-8).

no.	Tag Sequence	N-EC's	T-EC's	HUVEC	HMVEC	Cell Lines	Description
1	CATATCATTAA	247	501	130	87	2	angiomodulin (ANG, IGFBP-7, IGFBP-rP1, Mac25, TAF)
2	TGCACTTCAAG	328	141	0	0	0	hevin
3	TTTGCACCTTT	165	84	191	115	4	connective tissue growth factor (CTGF, IGFBP-rP2)
4	CCCTTGTCCG	131	104	1	1	0	ESTs
5	TTGCTGACTTT	73	131	2	14	1	collagen, type VI, alpha 1
6	ACCATTGGATT	102	67	0	0	2	interferon induced transmembrane protein 1 (9-27, Leu 13)
7	ACACTTCTTTC	104	44	60	62	2	guanine nucleotide binding protein 11
8	TTCTGCTCTTG	71	67	118	72	0	von Willebrand factor
9	TCCCTGGCAGA	68	68	3	13	3	cysteine-rich protein 2 (CRP-2, ESP-1, SmLIM)
10	TAATCCTCAAG	26	108	34	16	1	collagen, type XVIII, alpha 1
11	ATGTCTTTTCT	58	65	17	17	3	insulin-like growth factor-binding protein 4
12	GGGATTAAAGC	40	67	30	14	2	CD146 (S-Endo 1, P1H12, Muc18, MCAM, Mel-CAM)
13	TTAGTGTCGTA	38	69	9	13	0	SPARC (osteonectin, BM-40)
14	TTCTCCCAAAT	20	86	16	84	2	collagen, type IV, alpha 2
15	GTGCTAAGCGG	24	74	0	10	2	collagen, type VI, alpha 2
16	GTTTATGGATA	35	58	11	11	1	matrix Gla protein (MGP)
17	CCCTTTCACAC	52	33	0	0	0	ESTs, Weakly similar to HPBRII-7 protein
18	TGTTCTGGAGA	58	27	18	56	2	gap junction protein, alpha 1, 43kD (connexin 43)
19	AAGATCAAGAT	34	50	2	4	1	actin, alpha 1, skeletal muscle / actin, alpha 2, smooth muscle, aorta
20	TCTCTGAGCAT	32	48	0	0	0	aggrecanase 1 (metalloproteinase with thrombospondin type 1 motifs, 4)
21	CAGGTTTCATA	22	56	0	0	0	small inducible cytokine subfamily B (Cys-X-Cys), member 14 (BRAK)
22	GCACAAGTTCT	43	26	6	22	0	calcitonin receptor-like receptor activity modifying protein 2
23	AGCTTGTGGCC	45	23	0	0	0	calcitonin receptor-like receptor activity modifying protein 3
24	CTTCTGGATAA	13	54	12	0	0	cell division cycle 42 (GTP-binding protein, 25kD)
G1 25	CAACAATAATA	42	25	13	6	0	ESTs

26	ACCGGCGCCCG	50	15	0	0	0	tetranectin (plasminogen-binding protein)
27	GGAAGCTAAGT	35	27	0	5	1	osteoblast specific factor 2 (fasciclin I-like)
28	GCAATTTAACC	38	21	0	3	0	solute carrier family 21 (prostaglandin transporter), member 2
29	GATAACTACAT	18	35	4	4	0	angiomodulin (ANG, IGFBP-7, IGFBP-rP1, Mac25, TAF)
30	TATGAGGGTAA	19	30	40	2	0	regulator of G-protein signalling 5
31	CCACGGGATTC	10	39	0	0	0	collagen, type III, alpha 1
32	TTTACAAAGAG	28	21	0	1	1	carboxypeptidase E
33	CCCAGTAAGAT	22	25	0	16	1	cysteine and glycine-rich protein 2 (LIM domain only, smooth muscle)
34	ACAAAGCATTT	28	20	0	14	1	Human insulin-like growth factor binding protein 5 (IGFBP5) mRNA
35	GCCTGTCCCTC	8	38	22	11	0	ESTs / biglycan
36	TACTTTATAAG	25	21	1	1	0	metalloproteinase with thrombospondin type 1 motifs (ADAMTS1, METH-1)
37	TGTTTAATACA	15	29	2	1	1	ESTs / erythrocyte membrane protein band 4.1-like 2
38	GTCCCTGCCTT	18	25	1	1	0	glutathione S-transferase M2 (muscle)
39	GAGCCATCATA	21	21	2	2	1	ESTs / GTP-binding protein overexpressed in skeletal muscle
40	GGCCCTACAGT	26	13	2	3	0	ESTs / KIAA0821 protein
41	GCTAACCCCTG	7	31	0	1	0	ESTs
42	ATCACACAGCT	19	18	0	0	0	thyroid and eye muscle autoantigen D1 (64kD)
43	ACAAGTACTGT	18	19	38	27	0	cadherin 5, VE-cadherin (vascular epithelium)
44	TCACCGTGGAC	20	17	0	1	0	selectin P (granule membrane protein 140kD, antigen CD62)
45	ACATTCCAAGT	18	18	0	1	1	tissue inhibitor of metalloproteinase 3
46	GAGCCTGGATA	6	28	0	0	0	chondroitin sulfate proteoglycan 4 (melanoma-associated)
47	GGCACTCCTGT	22	13	19	12	0	ESTs
48	TCACAGCCCCC	20	15	8	5	0	ESTs
49	TGCCAGGTGCA	10	23	0	1	0	albumin
50	TGGGAAACCTG	11	22	0	1	1	eukaryotic translation initiation factor 4 gamma, 1
51	TTTCATCCACT	20	13	0	2	0	ESTs, KIAA0362 protein
52	AACAGGGGCCA	15	18	0	0	1	interferon, alpha-inducible protein (clone IFI-6-16)
53	ACTGAAAGAAG	6	26	0	0	1	complement component 1, s subcomponent
54	ACCGTTCTGTA	8	24	10	6	0	transcription factor 4
55	ATACTATAATT	25	6	12	0	0	ESTs
56	TTTGTATAGAA	17	15	4	5	1	hect domain and RLD 2
57	GTAATGACAGA	20	11	1	1	1	stanniocalcin
58	AATAGGGGAAA	13	19	4	1	0	ESTs, KIAA1075 protein
59	GTGCTACTTCT	5	25	2	18	0	collagen, type IV, alpha 1
60	CCGGCCCCTCC	6	24	0	0	1	peanut (Drosophila)-like 2
61	TTGAATTTGTT	19	10	1	1	0	RNA-binding protein gene with multiple splicing
62	CGAGAGTGTGA	22	6	0	0	0	ESTs
63	CCCTGTTCAGC	14	15	38	24	0	tyrosine kinase with IgG and EGF homology domains (Tie)

G1

64	CAGATGGAGGC	18	10	1	9	0	ESTs
65	AGGCTCCTGGC	8	20	0	0	0	ESTs
66	TCTGCTTCTAG	20	8	40	15	0	ESTs
67	GGCTTAGGATG	18	9	10	14	0	ESTs
68	GGTTGTTGCGG	6	21	0	0	1	ESTs
69	ACAAGTACCCA	5	22	4	5	0	P311 protein
70	CTTCTCTTGAG	18	9	1	4	1	basic transcription element binding protein 1
71	GCTAATAATGT	10	17	0	2	0	KIAA1077 protein
72	TGTGCTTTTTT	10	15	1	4	0	KIAA0758 protein / protein kinase, cAMP-dependent, catalytic, alpha
73	CATCACGGATC	17	8	0	1	0	interleukin 1 receptor, type I
74	GCAGCAGCAGC	6	18	0	2	0	T-box 2
75	TGACTGTATTA	13	11	0	0	0	ESTs / amine oxidase, copper containing 3 (vascular adhesion protein 1)
76	GAATGCTCTTG	6	18	0	11	0	gap junction protein, alpha 4, 37kD (connexin 37)
77	GTAGTTCTGGA	18	6	0	5	0	ESTs, clone 23698 mRNA
78	TCCCCTCTCTC	6	17	0	0	0	periodontal ligament fibroblast protein
79	GGGCAGTGGCT	5	18	12	5	0	ESTs, DKFZP586B0621 protein
80	AAATATGTGTT	19	4	13	3	0	ESTs
81	GTCATTTTCTA	11	11	10	2	0	transcription factor 8 (represses interleukin 2 expression)
82	CTCTCCAAACC	14	8	0	0	0	complement component 1 inhibitor (angioedema, hereditary)
83	TTAATGTGTAA	4	18	0	0	0	guanylate cyclase 1, soluble, beta 3
84	TCAAGCAATCA	13	9	0	1	0	ESTs
85	GAAGACACTTG	15	7	1	0	0	ESTs
86	GGGTAGGGTGA	6	15	0	0	1	integrin, alpha 7
87	TGGAACAGTGA	10	10	10	5	0	ESTs
88	GAGTGGCTACC	10	9	0	0	0	ESTs
89	GTCAGGGTCCC	13	7	0	9	0	decidual protein induced by progesterone
90	GTCAGTCACTT	14	8	4	1	0	hairy (Drosophila)-homolog
91	AGCAGAGACAA	14	8	1	10	0	natriuretic peptide receptor A - guanylate cyclase A
92	AGCGATGGAGA	9	10	0	0	0	ESTs
93	CGTGGGGTGTA	9	10	17	3	0	

TEM's complete web table

Table 2. SAGE tags elevated in tumor endothelium. The top 46 tags with the highest tumor EC (T-EC's) to normal EC (N-EC's) tag ratios are listed in descending order. To calculate tag ratios, a value of 0.5 was assigned in cases where zero tags were observed. The SAGE libraries are the same as those listed in Table 1. Tag numbers for each group were normalized to 100,000 transcripts. A 'Description' of the gene product corresponding to each tag is given, followed by alternative names in parenthesis. †; multiple tags for this gene are due to alternative polyadenylation sites.

no.	Tag Sequence	N-EC's	T-EC's	HUVEC	HMVEC	Cell Lines	Description
1	GGGGCTGCCCA	0	28	0	2	0	ESTs, similarity to thrombomodulin TEM1
2	GATCTCCGTGT	0	25	0	0	0	ESTs, similarity to rat Rhes ras-related protein TEM2
3	CATTTTTATCT	0	23	0	0	0	ESTs
4	CTTTCTTTGAG	0	22	6	20	1	regulated in glioma-like 7-1 (Dkk-3/ REIC)
5	TATTAACTCTC	0	21	1	3	1	ESTs, similarity to JNK interacting protein-3a
6	CAGGAGACCCC	0	16	2	0	0	MMP-11 (stromelysin 3)
7	GGAAATGTCAA	1	31	53	22	1	MMP-2 (gelatinase A, 72kD type IV collagenease)
8	CCTGGTTCAGT	0	15	0	0	0	ESTs
9	TTTTTAAGAAC	0	14	1	4	0	ESTs
10	TTTGGTTTTCC	5	139	0	16	0	collagen, type I, alpha 2, transcript A†
11	ATTTTGTATGA	0	13	4	8	0	nidogen (entactin)
12	ACTTTAGATGG	1	23	0	15	0	collagen, type VI, alpha 3
13	GAGTGAGACCC	3	63	0	0	1	Thy-1 cell surface antigen
14	GTACACACACC	0	10	0	0	0	ESTs / cystatin S
15	CCACAGGGGAT	2	38	0	2	1	collagen, type III, alpha 1
16	TTAAAAGTCAC	1	19	1	3	1	ESTs
17	ACAGACTGTTA	4	74	0	0	0	ESTs, similarity with sea squirt nidogen TEM7
18	CCACTGCAACC	1	18	0	1	0	
19	CTATAGGAGAC	1	18	1	1	0	ESTs, similarity with homeobox protein DLX-3 TEM8
20	GTTCCACAGAA	0	9	0	3	0	collagen, type I, alpha 2, transcript B†
21	TACCACCTCCC	0	9	4	1	1	ESTs / pregnancy specific beta-1-glycoprotein 1
22	GCCCTTTCTCT	1	17	3	1	2	endo180 lectin
23	TTAAATAGCAC	2	33	0	4	0	collagen, type I, alpha 1
24	AGACATACTGA	1	16	1	0	0	ESTs, DKFZP434G162 protein
25	TCCCCCAGGAG	1	16	0	0	0	bone morphogenetic protein 1 (metalloprotease)
26	AGCCCAAAGTG	0	8	0	0	0	
27	ACTACCATAAC	0	8	0	0	0	slit (Drosophila) homolog 3 (MEGF5)
28	TACAAATCGTT	0	8	0	0	0	KIAA0672 gene product

see table 2 from paper for G1, G2 or G3

all G3

G3

29	TTGGGTGAAAA	0	8	0	0	0	ESTs
30	CATTATCCAAA	0	8	0	0	0	integrin, alpha 1
31	AGAAACCACGG	0	8	2	7	0	collagen, type IV, alpha 1
32	ACCAAAACCAC	0	8	0	3	0	
33	TGAAATAAAC	0	8	3	1	1	
34	TTTGGTTTCC	1	15	0	0	0	ESTs
35	GTGGAGACGGA	1	15	1	2	1	ESTs
36	TTTGTGTTGTA	1	14	2	0	0	collagen, typeXII, alpha 1
37	TTATGTTTAAT	3	39	0	0	1	lumican
38	TGGAAATGACC	15	179	0	40	0	ESTs / collagen, type I, alpha 1
39	TGCCACACAGT	1	13	0	2	0	transforming growth factor, beta 3
40	GATGAGGAGAC	3	35	0	18	1	collagen, type I, alpha 2, transcript C†
41	ATCAAAGGTTT	2	23	0	0	0	ESTs, DKFZp564O222 mRNA
42	AGTCACATAGT	1	11	2	0	0	cell division cycle 42 (GTP-binding protein)
43	TTCGGTTGGTC	4	45	0	19	0	
44	CCCCACACGGG	2	21	0	0	0	ESTs
45	GGCTTGCCTTT	1	10	0	10	1	
46	ATCCCTTCCCG	1	10	1	0	0	peanut-like protein 1

Table 3. Detection of transcripts in various tumor types by RT-PCR and in situ hybridization (ISH). The "+" sign indicates the presence of a robust RT-PCR product or stong positive staining of vessels by in situ hybridization. The "-" sign indicates an undetectable signal by in situ hybridization or an absent or barely detectable transcript by RT-PCR. The "+/-" sign indicates a very weak signal in a limited number vessels by in situ hybridization.

		TEM1	TEM3	TEM4	TEM5	TEM7	TEM8	TEM9	vWF	Hevin
RT-PCR	Colon Nor.	-	-	-	-	-	-	-	+	ND
	Colon Tum.	+	+	+	+	+	+	+	+	ND
ISH	Colon Nor.	-	-	-	-	-	-	-	+	+
	Colon Tum.	+	+	+	+	+	+	+	+	+
	Liver Met.	+	+/-	+	+	+	+	+	+/-	ND
	Lung Tum.	+	ND	+	+	+	+	+	+	+
	Brain Tum.	+	ND	ND	ND	+	ND	ND	+	+*
	Corpus Lut.	+	+	+	+	+	-	+	+	+
	Wound	+	ND	+	ND	+/-	+/-	ND	+	+

* hevin was localized to both endothelial cells and malignant cells in brain tissue.
ND: not determined.

www.sagenet.org\angio\table3.htm (to be posted upon publication)

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Table 9. SAGE tags elevated in normal endothelium. The top 46 tags with the highest normal EC (N-EC's) to tumor EC (T-EC's) tag ratios are listed in descending order. To calculate tag ratios, a value of 0.5 was assigned in cases where zero tags were observed. The SAGE libraries are the same as those listed in Table 1. Tag numbers for each group were normalized to 100,000 transcripts. A 'Description' of the gene product corresponding to each tag is given, followed by alternative names in parenthesis.

no.	Tag Sequence	N-EC's	T-EC's	HUVEC	HMVEC	Cell Lines	Description
1	TCTCACGTCT	26	0	0	0	0	mucosal vascular addressin cell adhesion molecule 1
2	CTAGCGTTTT	19	0	4	14	0	serum deprivation response (phosphatidylserine-binding protein)
3	GTGGCTGACG	18	0	1	0	0	ESTs / intercellular adhesion molecule 4
4	CTCTTAAAAA	34	1	1	0	0	small inducible cytokine subfamily A (Cys-Cys), member 14
5	TGGGAAGAGG	16	0	3	4	1	ESTs
6	GTTTAAGGAT	16	0	0	0	0	ESTs
7	CTTTGTTTTG	15	0	56	32	1	endothelin 1 / ribosomal protein L27
8	ATTGCCAATC	14	0	0	4	0	TU3A protein
9	TGTTGAAAAA	21	1	1	0	0	selectin E (endothelial adhesion molecule 1)
10	ACAAAAAGGC	21	1	0	6	0	TU3A protein
11	AAGATGCACAC	21	1	1	1	1	phosphodiesterase I - nucleotide pyrophosphatase 2 (autotaxin)
12	GTAGAGGAAA	10	0	0	9	0	platelet/endothelial cell adhesion molecule (CD31 antigen)
13	TTGTTCAAGG	10	0	0	1	0	ESTs
14	CTCTTCAAAAA	19	1	1	0	0	ESTs / small inducible cytokine subfamily A, member 14
15	TATTAAAATA	18	1	8	9	1	transforming growth factor, beta receptor II (70-80kD)
16	GAATTCACCA	9	0	1	14	0	ESTs
17	AAGGAGAACT	9	0	0	0	0	small inducible cytokine subfamily A, member 14
18	AATATCTGAC	9	0	2	2	2	active BCR-related gene
19	TCAGTGACCAG	17	1	4	7	2	protein kinase C eta
20	GCAAAGTGCC	32	2	1	5	0	ESTs
21	TAAATACTTG	8	0	2	0	0	ESTs (2 unigene clusters)
22	GTCACTAATT	8	0	1	0	0	ESTs
23	ATAACCTGCA	8	0	0	0	0	signaling lymphocytic activation molecule
24	TGCATCTGTGC	46	3	1	1	0	ESTs / glycogenin 2
25	TAAAGGCACA	15	1	4	3	0	LIM binding domain 2
26	GACCGCGGCT	73	5	11	7	0	claudin 5
27	ACTCCGGTGT	14	1	0	8	0	ESTs

28	CTTCTCACCT	27	2	3	1	0	GTP-binding protein
29	TCGTGCTTTG	13	1	0	0	0	ESTs
30	GAGCAGTGCT	13	1	4	2	1	feline sarcoma viral (v-fes) - Fujinami avian sarcoma viral (v-fps) homolog
31	CTCTAAAAAA	10	1	0	1	0	ESTs
32	GAAACCCGGT	10	1	0	0	1	phospholipase C, beta 4
33	AACACAGTGC	10	1	7	15	1	ESTs